September 1991
Volume 36, Number 9
ISSN 00989142-RECACP

RESPIRATORY CARE

A MONTHLY SCIENCE JOURNAL
36TH YEAR—ESTABLISHED 1956

SPECIAL ISSUE

CONSENSUS CONFERENCE ON AEROSOL DELIVERY

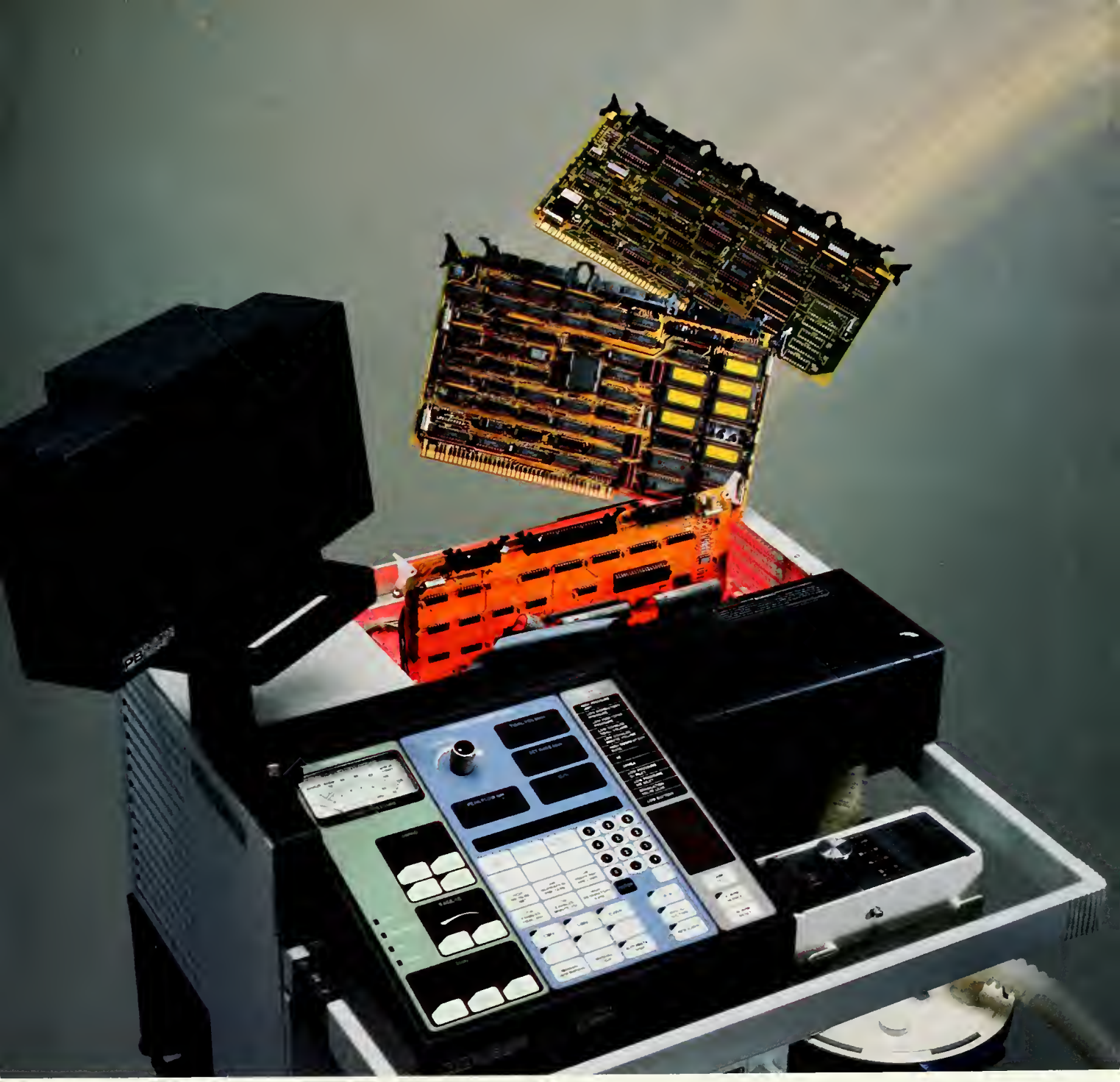
- Aerosol Consensus Statement—1991
- Advantages of the Aerosol Route
- Clinical Aspects of Aerosol Physics
- Aerosol Generators & Delivery Systems
- Patient & Aerosol Generator Interface
- Dosing Strategies for Aerosol
- Parenchymal Aerosol Therapy
- Aerosol Therapy in Children
- Escape of Aerosolized Medication into the Environment
- Control of TB during Aerosol Therapy
- Toxicology of Ribavirin & Pentamidine
- MDI Propellants: Environmental Impact

Unlimited Simplicity.

The new 7200® ae ventilator. A simplified keyboard. Easier-to-use. Easier-to-learn. It's as simple as that. If you'd like to learn more, that's easy too. Call 1-800-255-6773.

PB PURITAN BENNETT®

Circle 108 on reader service card



Simply Unlimited.

The new 7200® ae ventilator. A powerful new microprocessor for graphics, pressure control ventilation, and more. As always a quick, easy upgrade away. More options today . . . more tomorrow. Call 1-800-255-6773. It's that simple.

PB PURITAN BENNETT®

Circle 128 on reader service card

IN DEVELOPING OUR NEW PFT SYSTEM, WE ACHIEVED A SMALL GOAL.

You'll notice a sizable difference in our new ML Compact™ PFT system right away.

It offers a full range of tests, including flow-volume loops, slow VC, MVV, FRC via helium dilution, and single-breath DLCO testing.

Yet it's all contained in a small, PC-compatible package. So it fits in your office or lab easily.

It has a removable valve block that makes cleaning and sterilization significantly easier (flip a lever and the whole block drops into your hand).

And it uses Microsoft® Windows (just like our full-size MasterLab®), so if you can point and click with a mouse, you've cleared a major hurdle in mastering the system.

As for reports, with ML Compact you can design them to look the way you (and Medical Records) want them to. Put graphs and text anywhere — top, bottom, left, right. Create as many formats as you like.

To get the big picture, give us a call; we'll send a little information your way.

USA and Canada call toll free:
Domestic Sales **800/426-0347**, Canada Sales **800/633-2888**
2121 Terry Avenue; Seattle, WA 98121-2791
Telex 3794094 QUINTON SEA; FAX 206/223-8465

Quinton®
instrument co.

Microsoft is a registered trademark of Microsoft Corp.
MasterLab is a registered trademark of Erich Jaeger GmbH & Co. KG

Circle 105 on reader service card

RESPIRATORY CARE

A Monthly Science Journal. Established 1956. Official Journal of the American Association for Respiratory Care.

EDITORIAL OFFICE
11030 Ables Lane
Dallas TX 75229
(214) 243-2272

EDITOR
Pat Brougher RRT

ADJUNCT EDITOR
Philip Kittredge RRT

MANAGING EDITOR
Ray Masferrer RRT

EDITORIAL COORDINATOR
Donna Stephens

EDITORIAL BOARD
Neil MacIntyre MD, Chairman
Thomas A Barnes EdD RRT
Richard D Branson RRT
Robert L Chatburn RRT
Charles G Durbin Jr MD
Thomas D East PhD
Dean Hess MEd RRT
Robert M Kacmarek PhD RRT
David J Pierson MD
James K Stoller MD

CONSULTING EDITORS
Frank E Biondo BS RRT
Howard J Birenbaum MD
John G Burford MD
Bob Demers BS RRT
Douglas B Eden BS RRT
Donald R Elton MD
Robert R Fluck Jr MS RRT
Ronald B George MD
James M Hurst MD
Charles G Irvin PhD
MS Jastremski MD
Hugh S Mathewson MD
Michael McPeck BS RRT
Richard R Richard BS RRT
John Shigeoka MD
R Brian Smith MD
Jack Wanger RCPT RRT
Jeffrey J Ward MEd RRT

JOURNAL ASSOCIATES
Stephen M Ayres MD
Reuben M Chernack MD
Joseph M Civetta MD
John B Downs MD
Donald F Egan MD
Gareth B Gish MS RRT
George Gregory MD
Ake Grenvik MD
H Frederick Helmholz Jr MD
John E Hodgkin MD
William F Miller MD
Ellan J Nelson RN RRT
Thomas L Petty MD
Alan K Pierce MD
Henning Pontoppidan MD
John W Severinghaus MD
Barry A Shapiro MD

PRODUCTION STAFF
Donna Knauf
Jude Revoli
Jeannie Marchant

CONTENTS

September 1991
Volume 36, Number 9

SPECIAL ISSUE

CONSENSUS CONFERENCE ON AEROSOL DELIVERY

The Proceedings of a Conference
held January 10-12, 1991,
in Cancun, Mexico

EDITORIALS

914 Aerosol Therapy: The Hard Questions
by Sam P Giordano—Dallas, Texas

CONSENSUS STATEMENTS

916 Aerosol Consensus Statement—1991
by Consensus Conference Participants

CONFERENCE PROCEEDINGS

922 Clinical Advantages of the Aerosol Route of Drug Administration
by Nils Svedmyr—Gothenburg, Sweden

931 Clinical Aspects of Aerosol Physics
by Myrna Dolovich—Hamilton, Ontario, Canada

939 Aerosol Generators and Delivery Systems
by Stephen P Newman—Nottingham, United Kingdom

952 The Interface between Patient and Aerosol Generator
by Robert M Kacmarek and Dean Hess—Boston, Massachusetts and York, Pennsylvania

977 Dosing Strategies for Bronchodilator Aerosol Delivery
by Donald P Tashkin—Los Angeles, California

RESPIRATORY CARE (ISSN 00989142) is a monthly publication of Daedalus Enterprises, Inc, for the American Association for Respiratory Care. Copyright © 1991 by Daedalus Enterprises Inc, 11030 Ables Lane, Dallas TX 75229. All rights reserved. Reproduction in whole or in part without the express, written permission of Daedalus Enterprises, Inc, is prohibited. The opinions expressed in any article or editorial are those of the author and do not necessarily reflect the views of Daedalus Enterprises, Inc, the Editorial Board, or the American Association for Respiratory Care. Neither can Daedalus Enterprises, Inc, the Editorial Board, or the American Association for Respiratory Care be responsible for the consequences of the clinical applications of any methods or devices described herein.

RESPIRATORY CARE is indexed in *Hospital Literature Index* and in *Cumulative Index to Nursing* and *Allied Health Literature*.

Subscription Rates: $5.00 per copy; $50.00 per year (12 issues) in the US; $70.00 in all other countries (add $84.00 for air mail).

Second Class Postage paid at Dallas, TX. POSTMASTER: Send address changes to RESPIRATORY CARE, Daedalus Enterprises, Inc, 11030 Ables Lane, Dallas TX 75229.

Sleep Testing

Imagine the people you can reach, the needs you can fulfill.

CNS, Inc. 1250 Park Road, Chanhassen, MN 55317-9260. (800) 843-2978. In MN (612) 474-7600 In Europe: Erich Jaeger GmbH Germany, 0931/41902-0

Circle 117 on reader service card

MANUSCRIPT SUBMISSION
Instructions for Authors and Typists is printed near the end of every issue of RESPIRATORY CARE.

PHOTOCOPYING & QUOTATION
PHOTOCOPYING. Any material in this journal that is copyrighted by Daedalus Enterprises, Inc. may be photocopied for noncommercial purposes of scientific or educational advancement.

QUOTATION. Anyone may, without permission, quote up to 500 words of material in this journal that is copyrighted by Daedalus Enterprises, Inc., provided the quotation is for noncommercial use, and provided RESPIRATORY CARE is credited. Longer quotation requires written approval by the author and publisher.

SUBSCRIPTIONS/CHANGE OF ADDRESS
RESPIRATORY CARE
11030 Ables Lane
Dallas TX 75229
(214) 243-2272

SUBSCRIPTIONS. Individual subscription rates are $50.00 per year (12 issues) in the U.S. and Puerto Rico, $70.00 per year in all other countries; $95.00 for 2 years in the U.S. and Puerto Rico, $135.00 in all other countries; and $140.00 for 3 years in the U.S. and Puerto Rico, $200.00 in all other countries (add $84.00 per year for air mail). Annual organizational subscriptions are offered to members of associations according to their membership enrollment as follows: 101-500 members—$5.00, 501-1,500 members—$4.50, 1,501-2,500 members—$4.25, 2,501-5,000 members—$4.00, 5,001-10,000 members—$3.00, and over 10,000 members—$2.00. Singles copies, when available, cost $5.00; add $7.00 air mail postage to foreign countries overseas.

CHANGE OF ADDRESS. Six weeks notice is required to effect a change of address. Note your subscription number (from the mailing label), your name, and both old and new addresses, included zip codes. Please note your subscription number on the envelope. Copies will not be replaced without charge unless a request is received within 60 days of the mailing in the U.S. or within 90 days in other countries.

MARKETING DIRECTOR
Dale Griffiths

ADVERTISING ASSISTANT
Beth Binkley

ADVERTISING. Display advertising for the Journal should be arranged with the advertising representatives. RESPIRATORY CARE does not publish a classified advertising column.

ADVERTISING:
RATES AND MEDIA KITS
Aries Advertising Representatives
Saul Hornik
Sandy Getterman
12 Court St
Freehold NJ 07728
(201) 462-7422 or 972-1911

CONTENTS, *Continued*

September 1991
Volume 36, Number 9

989 Dosing Strategies for Aerosol Delivery to the Lung Parenchma, with Specific Recommendations for Pentamidine
by Heinrich Matthys and Rosa Herceg—Freiburg, Germany

994 Aerosol Therapy in Children
by R Michael Sly—Washington, District of Columbia

1008 Aerosol Exhaust: Escape of Aerosolized Medication into the Patient and Caregiver's Environment
by Robert J Fallat and Kathryn Kandal—San Francisco, California

1017 Control of Tuberculosis during Aerosol Therapy Administration
by Richard E Chaisson and Sharon McAvinue—Baltimore, Maryland

1026 Toxicology of Antimicrobial Aerosols: A Review of Aerosolized Ribavirin and Pentamidine
by Hetty Waskin—Durham, North Carolina

1037 Propellant Gases in Metered Dose Inhalers: Their Impact on the Global Environment
by John R Balmes—San Francisco, California

ABSTRACTS
899 Summaries of Pertinent Articles in Other Journals

CALENDAR OF EVENTS
1046 Meeting Dates, Locations, Themes

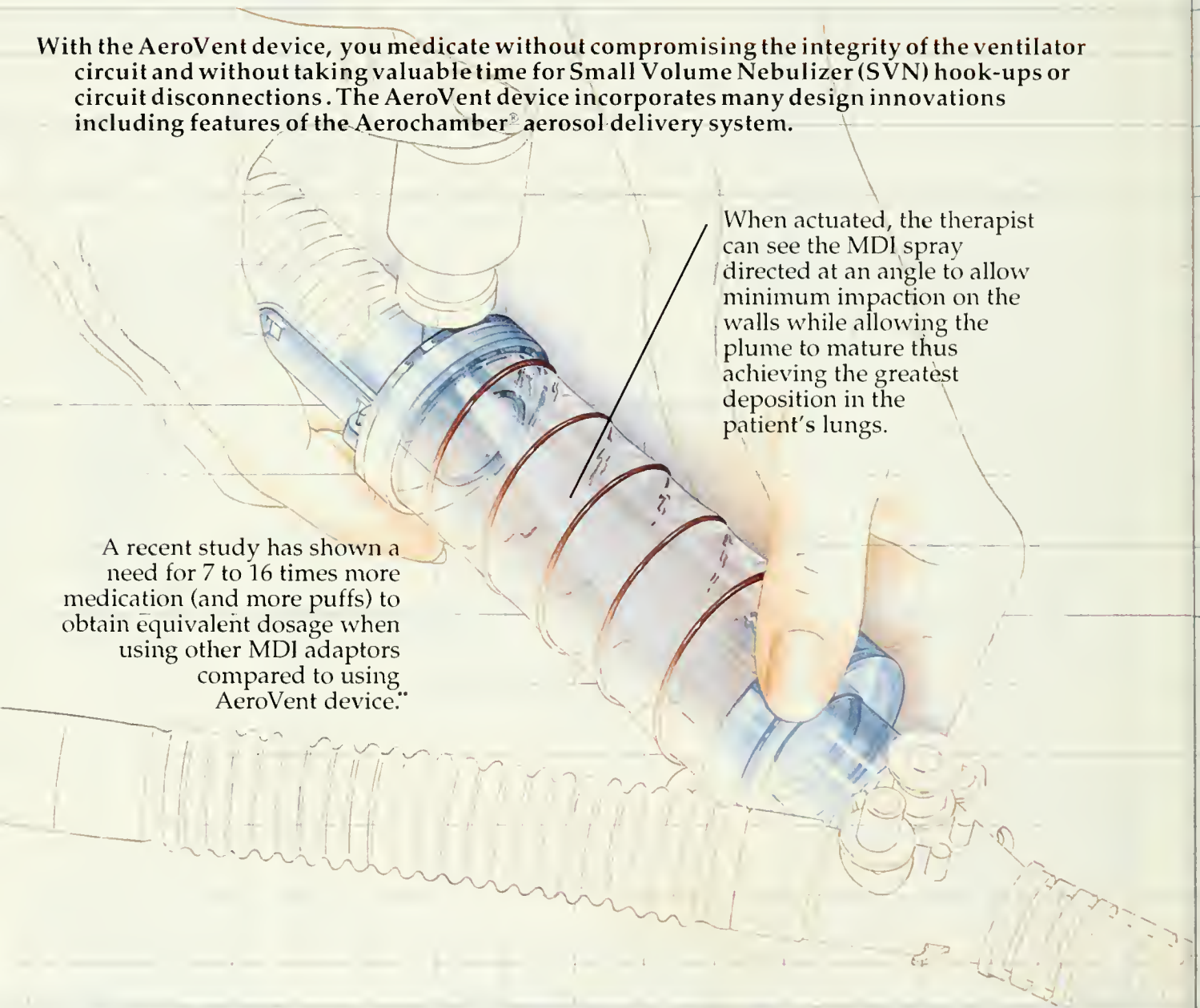
NOTICES
1051 Examination Dates, Notices, Prizes

INFORMATION FOR AUTHORS
1053 Instructions for Authors and Typists

INDEXES
1056 Authors in This Issue
1056 Advertisers in This Issue
1050 Advertiser Help Lines

Designed to Deliver
Directly to the

With the AeroVent device, you medicate without compromising the integrity of the ventilator circuit and without taking valuable time for Small Volume Nebulizer (SVN) hook-ups or circuit disconnections. The AeroVent device incorporates many design innovations including features of the Aerochamber® aerosol delivery system.



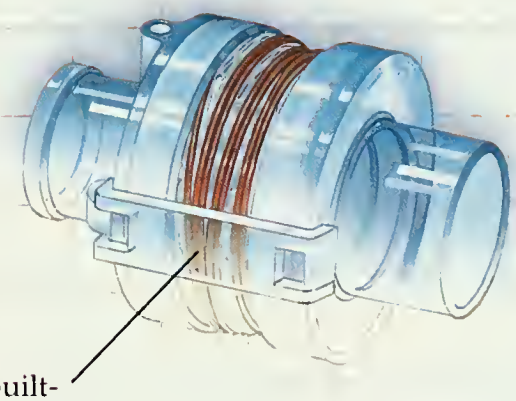
When actuated, the therapist can see the MDI spray directed at an angle to allow minimum impaction on the walls while allowing the plume to mature thus achieving the greatest deposition in the patient's lungs.

A recent study has shown a need for 7 to 16 times more medication (and more puffs) to obtain equivalent dosage when using other MDI adaptors compared to using AeroVent device.**

** Metered Dose Inhaler Actuator-Adapters: A Comparison of Particle Size and Drug Delivery Through an Endotracheal Tube - Richard P. Larson, RRT et all - Resp. Care Nov '89 Vol 34 No 11

The AeroVent device is designed for convenient single patient use.

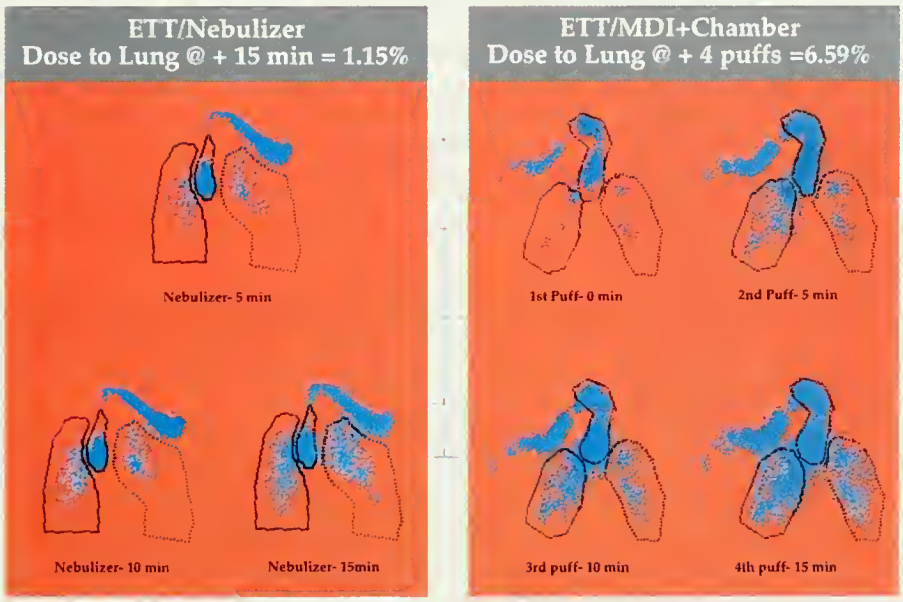
Aerosol Medications Ventilated Patient.



The AeroVent holding chamber can be latched when collapsed in the circuit, ready for the next time you need to medicate the patient. Simply unlatch, expand the AeroVent device and actuate the aerosol medication from the metered dose inhaler (MDI).

The AeroVent device includes a built-in snap closure to keep the AeroVent collapsed while in place and not in use, allowing unrestricted gas flow through the breathing circuit.

The AeroVent device has been tested and proven to deliver 4.5 times greater deposition than a standard SVN to the mechanically ventilated patient. *



Graphic Representation of Actual Lung Deposition Data.

* Fuller HD, Dolovich MB, Posmituck G, Wong Pack W. and Newhouse MT. Pressurized Aerosol versus Jet Aerosol Delivery to Mechanically Ventilated Patients: Comparison of dose to the lungs. Am Rev Respir Dis; 141:440-444

monaghan

MONAGHAN MEDICAL CORPORATION

P.O. Box 2805, Plattsburgh, NY 12901
800-833-9653 / 518-561-7330
Fax: 518-561-5660

Circle 142 on reader service card

New!

Now Available!

SURVANTA®

beractant

intratracheal suspension

From Ross Laboratories—
Helping Premature Babies Survive™

Please see adjacent column for Brief Summary of prescribing information.

A8688/1970
© 1991 Ross Laboratories

ROSS LABORATORIES
COLUMBUS, OHIO 43216
Division of Abbott Laboratories, USA

LITHO IN USA

Circle 124 on reader service card

BRIEF SUMMARY: Please see package insert for full prescribing information.

SURVANTA® (1040)

beractant
intratracheal suspension
Sterile Suspension/For Intratracheal Use Only

INDICATIONS AND USAGE
SURVANTA is indicated for prevention and treatment ("rescue") of Respiratory Distress Syndrome (RDS) (hyaline membrane disease) in premature infants. SURVANTA significantly reduces the incidence of RDS, mortality due to RDS and air leak complications.

Prevention
In premature infants less than 1250 g birth weight or with evidence of surfactant deficiency, give SURVANTA as soon as possible, preferably within 15 minutes of birth.

Rescue
To treat infants with RDS confirmed by x-ray and requiring mechanical ventilation, give SURVANTA as soon as possible, preferably by 8 hours of age.

CONTRAINDICATIONS
None known.

WARNINGS
SURVANTA is intended for intratracheal use only.

SURVANTA CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE. Therefore, its use should be restricted to a highly supervised clinical setting with immediate availability of clinicians experienced with intubation, ventilator management, and general care of premature infants. Infants receiving SURVANTA should be frequently monitored with arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.

DURING THE DOSING PROCEDURE, TRANSIENT EPISODES OF BRADYCARDIA AND DECREASED OXYGEN SATURATION HAVE BEEN REPORTED. If these occur, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After stabilization, resume the dosing procedure.

PRECAUTIONS
General
Rales and moist breath sounds can occur transiently after administration. Endotracheal suctioning or other remedial action is not necessary unless clear-cut signs of airway obstruction are present.

Increased probability of post-treatment nosocomial sepsis in SURVANTA-treated infants was observed in the controlled clinical trials (Table 3). The increased risk for sepsis among SURVANTA-treated infants was not associated with increased mortality among these infants. The causative organisms were similar in treated and control infants. There was no significant difference between groups in the rate of post-treatment infections other than sepsis.

Use of SURVANTA in infants less than 600 g birth weight or greater than 1750 g birth weight has not been evaluated in controlled trials. There is no controlled experience with use of SURVANTA in conjunction with experimental therapies for RDS (eg, high-frequency ventilation or extracorporeal membrane oxygenation).

No information is available on the effects of doses other than 100 mg phospholipids/kg, more than four doses, dosing more frequently than every 6 hours, or administration after 48 hours of age.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Reproduction studies in animals have not been completed. Mutagenicity studies were negative. Carcinogenicity studies have not been performed with SURVANTA.

ADVERSE REACTIONS
The most commonly reported adverse experiences were associated with the dosing procedure. In the multiple-dose controlled clinical trials, transient bradycardia occurred with 11.9% of doses. Oxygen desaturation occurred with 9.8% of doses.

Other reactions during the dosing procedure occurred with fewer than 1% of doses and included endotracheal tube reflux, pallor, vasoconstriction, hypotension, endotracheal tube blockage, hypertension, hypocarbia, hypercarbia, and apnea. No deaths occurred during the dosing procedure, and all reactions resolved with symptomatic treatment.

The occurrence of concurrent illnesses common in premature infants was evaluated in the controlled trials. The rates in all controlled studies are in Table 3.

TABLE 3

	All Controlled Studies		
Concurrent Event	**SURVANTA (%)**	**Control (%)**	***P*-Value[a]**
Patent ductus arteriosus	46.9	47.1	0.814
Intracranial hemorrhage	48.1	45.2	0.241
Severe intracranial hemorrhage	24.1	23.3	0.693
Pulmonary air leaks	10.9	24.7	<0.001
Pulmonary interstitial emphysema	20.2	38.4	<0.001
Necrotizing enterocolitis	6.1	5.3	0.427
Apnea	65.4	59.6	0.283
Severe apnea	46.1	42.5	0.114
Post-treatment sepsis	20.7	16.1	0.019
Post-treatment infection	10.2	9.1	0.345
Pulmonary hemorrhage	7.2	5.3	0.166

[a]*P*-value comparing groups in controlled studies

When all controlled studies were pooled, there was no difference in intracranial hemorrhage. However, in one of the single-dose rescue studies and one of the multiple-dose prevention studies, the rate of intracranial hemorrhage was significantly higher in SURVANTA patients than control patients (63.3% *v* 30.8%, $P = 0.001$; and 48.8% *v* 34.2%, $P = 0.047$, respectively). The rate in a Treatment IND involving approximately 4400 infants was lower than in the controlled trials.

In the controlled clinical trials, there was no effect of SURVANTA on results of common laboratory tests: white blood cell count and serum sodium, potassium, bilirubin, creatinine.

More than 3700 pretreatment and post-treatment serum samples were tested by Western Blot immunoassay for antibodies to surfactant-associated proteins SP-B and SP-C. No IgG or IgM antibodies were detected.

Several other complications are known to occur in premature infants. The following conditions were reported in the controlled clinical studies. The rates of the complications were not different in treated and control infants, and none of the complications were attributed to SURVANTA.

Respiratory: lung consolidation, blood from the endotracheal tube, deterioration after weaning, respiratory decompensation, subglottic stenosis, paralyzed diaphragm, respiratory failure

Cardiovascular: hypotension, hypertension, tachycardia, ventricular tachycardia, aortic thrombosis, cardiac failure, cardiorespiratory arrest, increased apical pulse, persistent fetal circulation, air embolism, total anomalous pulmonary venous return

Gastrointestinal: abdominal distention, hemorrhage, intestinal perforations, volvulus, bowel infarct, feeding intolerance, hepatic failure, stress ulcer

Renal: renal failure, hematuria

Hematologic: coagulopathy, thrombocytopenia, disseminated intravascular coagulation.

Central Nervous System: seizures

Endocrine/Metabolic: adrenal hemorrhage, inappropriate ADH secretion, hyperphosphatemia.

Musculoskeletal: inguinal hernia

Systemic: fever, deterioration.

Follow-Up Evaluations
To date, no long-term complications or sequelae of SURVANTA therapy have been found.

Single-Dose Studies
Six-month adjusted-age follow-up evaluations of 232 infants (115 treated) demonstrated no clinically important differences between treatment groups in pulmonary and neurologic sequelae, incidence or severity of retinopathy of prematurity, rehospitalizations, growth, or allergic manifestations.

Multiple-Dose Studies
Six-month adjusted age follow-up evaluations have not been completed. Preliminarily, in 605 (333 treated) of 916 surviving infants, there are trends for decreased cerebral palsy and need for supplemental oxygen in SURVANTA infants. Wheezing at the time of examination tended to be more frequent among SURVANTA infants, although there was no difference in bronchodilator therapy.

Twelve-month follow-up data from the multiple-dose studies have been completed in 328 (171 treated) of 909 surviving infants. To date no significant differences between treatments have been found, although there is a trend toward less wheezing in SURVANTA infants in contrast to the six month results.

OVERDOSAGE
Overdosage with SURVANTA has not been reported. Based on animal data, overdosage might result in acute airway obstruction. Treatment should be symptomatic and supportive.

Rales and moist breath sounds can transiently occur after SURVANTA is given, and do not indicate overdosage. Endotracheal suctioning or other remedial action is not required unless clear-cut signs of airway obstruction are present.

HOW SUPPLIED
SURVANTA (beractant) Intratracheal Suspension is supplied in single-use glass vials containing 8 mL of SURVANTA (NDC 0074-1040-08). Each milliliter contains 25 mg of phospholipids (200 mg phospholipids/8 mL) suspended in 0.9% sodium chloride solution. The color is off-white to light brown.

Store unopened vials at refrigeration temperature (2-8°C). Protect from light. Store vials in carton until ready for use. Vials are for single use only. Upon opening, discard unused drug.

June, 1991

A8688/1970

ROSS LABORATORIES
COLUMBUS, OHIO 43216
Division of Abbott Laboratories USA

Circle 124 on Card

How You Can Help Patients Stop Smoking

The National Heart, Lung, and Blood Institute has made available "How You Can Help Patients Stop Smoking: Opportunities for Respiratory Care Practitioners." This guide was developed in collaboration with the AARC and provides guidance on talking to patients about smoking. Plus, it tells you how to integrate a smoking intervention program into a respiratory care department. Includes strategies for community outreach and information on smoking intervention techniques and tools.

Single copies are free of charge by calling or writing

The National Heart, Lung, and Blood Institute Education Programs Information Center
4733 Bethesda Avenue,
Suite #530
Bethesda, MD 20814
(301) 951-3260

Yours free!

PUBLIC RELATIONS With Your Peers

The best public relations you can achieve with your peers comes from proving you are the "consummate professional" and that you provide the best patient care possible.

PUBLIC RELATIONS Begin With You

American Association For Respiratory Care

11030 Ables Lane • Dallas, TX 75229-4593

(214) 243-2272

The MiniCAP™ 100 CO_2 Monitor eliminates the two biggest problems in modern capnometry —calibration drift and fluid contamination.

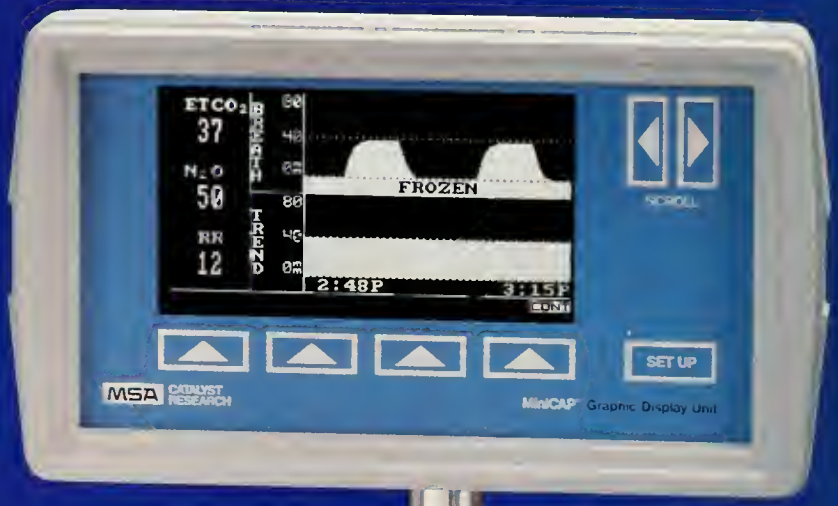
The CO_2 monitor for every ICU ventilator.

Calibration accuracy is guaranteed with a *two-year calibration warranty.* Such enduring accuracy results from a high stability sensor design and a patented drift correction technique. CO_2 readings are automatically compensated for the peak airway pressure, PEEP, CPAP, and pressure support, as well as for barometric pressure and N_2O.

The MiniCAP 100 CO_2 Monitor's fluid handling is superior, too. It features a minimal dead space fluid reservoir and fiber optics sensing that purges fluids into the reservoir, which alarms when full.

The optional MiniCAP Graphic Display Unit provides waveforms, 24-hour trend information, and digital display of CO_2, respiration rate, and mean N_2O. The unit interfaces easily with an Epson® FX graphics-type printer for hard copy of waveforms.

For complete details on the CO_2 monitor you can use with confidence, call **1-800-672-4678**, Ext. 8826.



MSA CATALYST RESEARCH

3706 Crondall Lane
Owings Mills, MD 21117 USA
301/356-2400
FAX: 301/581-0346

Epson is a registered trademark of Seiko Epson Corporation.

Circle 122 on reader service card

Reviews, Editorials, & Statements To Note

Respiratory Syncytial Virus from Chimps with Colds to Conundrums and Cures (editorial)—CB Hall, JT McBride. N Engl J Med 1991;325:57. (Pertains to Smith, Frankel, et al paper abstracted below.)

Catheter-Related Infections and Associated Septicemia (review)—S Norwood, A Ruby, J Civetta, V Cortes. Chest 1991;99:968.

Inhalation of the Cap of a Metered-Dose Inhaler (letter)—JTC Li. N Engl J Med 1991;325:431.

Inhalation of a Coin and a Capsule from Metered-Dose Inhalers (letter)—CH Schultz, SW Hargarten, J Babbitt. N Engl J Med 1991;325:431.

A Controlled Trial of Aerosolized Ribavirin in Infants Receiving Mechanical Ventilation for Severe Respiratory Syncytial Virus Infection—DW Smith, LR Frankel, LH Mathers, ATS Tang, RL Ariagno, CG Prober. N Engl J Med 1991;325:24.

Although the antiviral agent ribavirin improves the course of lower respiratory tract disease in spontaneously breathing infants with respiratory syncytial virus infection, it is not known whether ribavirin can benefit infants with severe respiratory syncytial virus disease who require mechanical ventilation. **Methods:** We conducted a randomized, double-blind, placebo-controlled evaluation of ribavirin (20 mg/mL) administered continuously in aerosolized form to infants receiving mechanical ventilation for respiratory syncytial virus infection. **Results**: Of the 28 infants (mean [SD] age 1.4 [1.7] months) enrolled, 7 had underlying diseases predisposing them to severe infection (mean age 3.0 [2.6] months), and 21 were previously normal (mean age 0.8 [0.9] month). Among the 14 infants who received ribavirin, the mean duration of mechanical ventilation was 4.9 days (as compared with 9.9 days among the 14 who received placebo; $p = 0.01$), and the mean length of supplemental oxygen use was 8.7 days (as compared with 13.5 days; $p = 0.01$). The mean length of the hospital stay was 13.3 days after treatment with ribavirin and 15.0 with placebo ($p = 0.04$). When only the 21 previously normal infants were considered, the mean-length of the hospital stay was 9.0 days for the ribavirin recipients and 15.3 days for those who received placebo ($p = 0.005$). **Conclusions**: In infants who require mechanical ventilation because of severe respiratory syncytial virus infection, treatment with aerosolized ribavirin decreases the duration of mechanical ventilation, oxygen treatment, and the hospital stay.

Treatment with Acyclovir of Varicella Pneumonia in Pregnancy—RC Broussard, DK Payne, RB George. Chest 1991;99:1045.

Varicella pneumonia during pregnancy carries a significant mortality for both mother and fetus. The antiviral drug, acyclovir, appears to have decreased mortality in reported cases. We present a case report and review of the literature summarizing the experience to date with acyclovir in the treatment of varicella pneumonia during pregnancy.

A Double-Blind Trial of a 16-Hour Transdermal Nicotine Patch in Smoking Cessation—P Tonnesen, J Norregaard, K Simonsen, U Säwe. N Engl J Med 1991;325:311.

The use of nicotine chewing gum combined with psychological support improves the success rate in quitting smoking. We studied the safety and efficacy of a transdermal nicotine patch in smoking cessation. **Methods**: We conducted a double-

New

2500 VOLDYNE®

Volumetric Incentive Deep-Breathing Exerciser

The accuracy of Voldyne, in a new size, matched to geriatric patients and patients with smaller lung capacities.

Voldyne 2500 ...

- A smaller, lighter flow cup **reduces the work of breathing**, thus improving patient performance and progress.
- Every unit is **individually tested and calibrated** for performance, reliability and superior accuracy of inhaled lung volume.
- Volume incentive spirometry **improves assessment of patient progress** by eliminating the guesswork associated with spirometers that only measure flow.
- Graduations printed on both sides of the unit allow the therapist to conveniently **observe volumes while instructing and encouraging the patient.**

For further information, contact your Sherwood O.R./Critical Care Representative or call:

1-800-325-7472 (outside Missouri)

1-800-392-7318 (in Missouri)

©1991 Sherwood Medical Company

Sherwood MEDICAL
ST LOUIS MO 63103 U.S.A.

Circle 125 on reader service card

blind randomized study comparing the effects of a 16-hour nicotine patch (15 ± 3.5 mg of nicotine in 16 hours) with those of a placebo patch. Of the 289 smokers (207 women and 82 men) enrolled in the study, 145 were treated with nicotine patches and 144 with placebo patches for 16 weeks. **Results**: Rates of sustained abstinence were significantly better with active treatment than with placebo: 53, 41, 24, and 17 % of those in the nicotine-patch group were abstinent after 6, 12, 26, and 52 weeks, respectively, as compared with 17, 10, 5, and 4 % of those in the placebo-patch group ($p < 0.0001$). Only two subjects with the nicotine patch and one with the placebo patch had to withdraw from the study because of side effects. **Conclusions**: The nicotine skin patch proved to be safe and effective, as demonstrated by a higher rate of abstinence than with placebo. However, the absolute rate of abstinence after 1 year was only 17%, which is lower than the rate in studies that have combined the use of nicotine chewing gum with behavioral therapy.

Comparison of a β_2 Agonist, Terbutaline, with an Inhaled Corticosteroid, Budesonide, in Newly Detected Asthma—T Haahtela, M Järvinen, T Kava, K Kiviranta, S Koskinen, K Lehtonen, et al. N Engl J Med 1991;325:388.

The presence of airway inflammation even in mild asthma points to the potential value of anti-inflammatory therapy. We compared the effect of inhaled corticosteroid, budesonide, with that of an inhaled β_2 agonist, terbutaline, in the long-term treatment of newly detected asthma. **Methods**: We studied 103 patients (29 male and 74 female patients 15 to 64 years old) in whom asthma had appeared within the previous year. The patients were randomly assigned in blinded fashion to two treatment groups: one to receive 600 μg of inhaled budesonide twice a day, and the other to receive 375 μg of inhaled terbutaline twice a day. The study period was two years. **Results**: After 6 weeks of treatment, the patients treated with budesonide tolerated inhaled histamine better than the patients treated with terbutaline (a difference of one doubling dose step, $p < 0.001$), and the difference was sustained. Patients' diaries kept during the first 3 months of the study and during the last month of the first and second years showed budesonide to be more effective than terbutaline in improving peak expiratory flow in the morning (average increase from the pretreatment value, 32.8 L/min for budesonide vs 4.8 L/min for terbutaline; $p < 0.001$) and in the evening ($p < 0.01$). Budesonide was also more effective in reducing the symptoms of asthma ($p < 0.01$) and the use of supplemental β_2 agonist medication ($p < 0.01$). Ten patients were withdrawn from the terbutaline group because treatment was insufficiently effective, whereas only one dropped out of the budesonide group. The adverse reactions to both treatments were few and mild. **Conclusions**: Anti-inflammatory therapy with inhaled budesonide is an effective first-line treatment for patients with newly detected, mild asthma, and it is superior to the use of terbutaline in such patients.

Obstructive Sleep Apnea following Topical Oropharyngeal Anesthesia in Loud Snorers—GA Chadwick, P Crowley, MX Fitzgerald, RG O'Regan, WT McNicholas. Am Rev Respir Dis 1991;143:810.

Previous studies support the presence of an upper airway reflex mechanism that contributes to the maintenance of upper airway patency during sleep. We investigated the possibility that interference with this reflex mechanism contributes to the development of obstructive sleep apnea. Eight otherwise asymptomatic snorers (7 male and 1 female), age 39 ± 5.3 y (mean ± SEM), underwent overnight sleep studies on three successive nights. An acclimatization night was followed by two study nights randomly assigned to control (C) and oropharyngeal anesthesia (OPA). On the OPA night topical anesthesia was induced using 10% lidocaine spray and 0.25% bupivocaine gargle. A saline placebo was used on Night C. All subjects slept well on both study nights (mean sleep duration was 6.2 h on both study nights), and sleep stage distribution was similar on both nights. Obstructive apneas and hypopneas (OAH) rose from 114 ± 43 during C to 170 ± 49 during OPA ($p < 0.02$). Central apneas and hypopneas (CAH) were unchanged between the two nights (8 ± 4.9 vs 7 ± 3). The duration of OAH was similar on both study nights (20 ± 1.9 s during C vs 20 ± 1.5 s during OPA). The frequency of movement arousals terminating OAH tended to be higher during OPA (7 ± 2.9/h) than during C (3 ± 0.7), p = NS. The frequency of oxyhemoglobin desaturations was also higher during OPA (5 ± 2.1/h) than during C (3 ± 1.4), $p < 0.07$. These data indicate that OPA increases the frequency of OAH during sleep but not their duration, suggesting that defective upper airway reflexes may influence the inhalation of obstructive respiratory events but not their termination. We conclude that upper airway reflexes are important in the pathophysiology of OSA.

Lung Function and Bronchial Reactivity in Asthmatics during Exposure to Volatile Organic Compounds—H Harving, R Dahl, L Molhave. Am Rev Respir Dis 1991; 143:751.

The purpose of the present study was to investigate whether vapors of organic solvents at low concentrations

could exert an adverse effect in the lower airways. Under controlled conditions in a climate chamber, 11 persons with bronchial hyperreactivity to histamine and bronchial asthma were exposed for 90 min to a mixture of organic solvents at levels of 0, 2.5, and 25 mg/m^3. During exposure to 25 mg/m^3 a decrease in FEV_1 to 90.7% of baseline value was measured. This was significantly different from the initial value ($p < 0.05$), but not significantly different from the value found after sham exposure (FEV_1, 97.4% of initial value). The decline in FEV_1 during exposure to 25 mg/m^3 was most pronounced in persons with high bronchial sensitivity. No changes were found in histamine reactivity after exposure, and no late reactions were registered. Ratings of discomfort showed different individual patterns ranging from no response to reactions towards both of the concentrations. The ratings indicated development of tolerance during exposure. Volatile organic compounds in concentrations found in both the work and the home environments may influence lung function and are probably of importance as bronchial irritants.

The Effect of Nightly Nasal CPAP Treatment on Underlying Obstructive Sleep Apnea and Pharyngeal Size—NA Collop, AJ Block, D Hellard. Chest 1991;99:855.

Nasal continuous positive airway pressure (CPAP) is an effective treatment for obstructive sleep apnea (OSA). It is usually prescribed for nightly use; however, recent studies show that patients often do not wear the appliance consistently. Previous studies have also suggested that nasal CPAP may improve a patient's underlying OSA even when the mask is not in place. We investigated 12 men with OSA to see if nasal CPAP used nightly for 6 weeks would improve their underlying sleep-disordered breathing. We also studied pharyngeal volumes measured using magnetic resonance imaging and a computer-controlled digitizing pad. Patients with more severe OSA had improvement after 6 weeks; however, they still demonstrated significant OSA. Patients with less severe OSA did not have significant change. We were unable to show a significant difference in any patient's awake pharyngeal volumes. We conclude that patients with OSA should be encouraged to wear their nasal CPAP machines regularly.

Great Vein and Right Atrial Thrombosis in Critically Ill Infants and Children with Central Venous Lines—W Berman Jr, RR Fripp, SM Yabek, J Wernly, S Corlew. Chest 1991;99:963.

We performed a retrospective review of echocardiographic data files of infants and children hospitalized in the Newborn and Pediatric Intensive Care Units. Echocardiograms were examined to detect the presence and evolution of great vein and right atrial thrombosis in patients with central venous lines. Thirty-seven patients were identified over a 5-year period. Echocardiograms were performed, not routinely but in response to specific indications including catheter malfunction, thrombocytopenia, persistent chylothorax, bacterial or fungal sepsis, and superior vena cava syndrome. Fifteen of 37 patients died, 13 of them during the hospitalization in which the thrombus was discovered. Thrombolytic agents and surgery were used to treat selected patients, with mixed results. Two of the 22 survivors have significant disability related to the thrombus or complications arising from it. We conclude that great vein and/or right artial thrombosis is a common complication of central venous catheterization in small infants and children; moreover, the morbidity and mortality relating to this complication is substantial.

Medication Adherence Patterns in Chronic Obstructive Pulmonary Disease—JJ Dolce, C Crisp, B Manzella, JM Richards, JM Hardin, WC Bailey. Chest 1991;99:837.

While medical treatment of COPD has advanced, the failure to adhere to regimens for medication poses a significant barrier to effective management. Furthermore, no data are available regarding adherence for patients within the United States. Data from this investigation indicate that 78 outpatients from a medical center in the southeastern region of the United States were prescribed an average of 6.26 medications with both various dosing schedules and different modes of administration. Adherence was poor, with 42 patients (54%) underutilizing medications, 39 patients (50%) overutilizing medications during periods of respiratory distress, and 24 patients (31%) employing ineffective inhaler dosing techniques. Prescription patterns and adherence were not associated with demographic variables; however, adherence was related to classes of medication and situational variables.

Predictors of Improvement in the 12-Minute Walking Distance following a 6-Week Outpatient Pulmonary Rehabilitation Program—RL ZuWallack, K Patel, JZ Reardon, BA Clark III, EA Normandin. Chest 1991;99:805.

We evaluated the relationship of clinical characteristics, pulmonary function, and exercise test data to the degree of improvement in the 12-min walking distance (12MD) in 50 ambulatory outpatients completing a 6-week pulmonary rehabilitation program. The 12MD increased by 27.7 ± 32.5 %, or 462 ± 427 ft, by the end

NEW!

ALP OPTI-MOL™ RESERVOIRS . . .

the alternative

*You now have an **alternative** source* for humidifier reservoirs that offers real savings, high performance, and dependable deliveries.

CAT NO AL8500
OPTI-MOL™
STERILE WATER
1550 mL FOR INHALATION, U S P
Sterile • Preservative Free • Nonpyrogenic
DISPOSABLE – SINGLE PATIENT USE
CAUTION Federal law restricts this device to sale by or on the order of a physician or licensed practitioner
AUTOMATIC LIQUID PACKAGING, INC.
concha ther
SERVO CONTROLLED HEATER
RESPIRATORY CARE INC
ha therm III
ROLLED HEATER CAT NO 300-80
RCI

ALP OPTI-MOL™ Reservoirs are interchangeable with CONCHA-PAK®* sterile water reservoirs. Perfectly placed puncture pin ports (top and bottom) align exactly with CONCHA-COLUMN®* canisters. The performance characteristics of your CONCHAPAK®* System is not compromised in any way. The same water level is maintained within the column as within the reservoir for high humidity.

ALP is represented in your area by the leading respiratory/anesthesia specialty dealer.

Automatic Liquid Packaging, Inc.
Healthcare Products Division
2200 West Lake Shore Drive
Woodstock, Illinois 60098 U.S.A.
Tel. (815) 338-9500
Tel. (800) 638-9778
Fax (815) 338-5504

* CONCHA-COLUMN AND CONCHAPAK ARE REGISTERED TRADEMARKS OF HUDSON RCI

© 1990 AUTOMATIC LIQUID PACKAGING, INC.

Circle 116 on reader service card

of the program. There were no significant relationships between improvement in the 12MD and age, sex, oxygen requirement, arterial blood gas levels, and pulmonary function; however, patients with a greater ventilatory reserve ($1 - [\dot{V}_{Emax}/MVV] \times 100$) had more improvement in their 12MD, both with respect to distance and percentage of increase over baseline. Additionally, patients with a lower peak oxygen consumption ($\dot{V}_{O_2}$) and peak oxygen pulse (O_2P) showed greater percentage of improvement in their 12MD. The magnitude of the initial 12MD was inversely related to its improvement, both with regard to distance ($r = -0.43$; $r^2 = 0.18$; $p < 0.003$) and percentage of increase ($r = -0.71$; $r^2 = 0.51$; $p < 0.0001$). Using stepwise regression, the combination of smaller initial 12MD and greater FEV_1 was significantly predictive of improvement in the 12MD. Patients with poor performance on either a 12MD or maximal exercise test are not necessarily poor candidates for a pulmonary rehabilitation program.

Respiratory Symptoms and Risk Factors in an Arizona Population Sample of Anglo and Mexican-American Whites—C Di Pede, G Viegi, JJ Quackenboss, P Boyer-Pfersdorf, MD Lebowitz. Chest 1991;99:916.

Prevalence rates of respiratory symptoms and diseases in a large group of Anglos and Mexican-Americans were analyzed. Each subject completed a questionnaire. Among current smokers, chronic productive cough and dyspnea were significantly higher in both ethnic groups; wheezy symptoms were higher in Anglos. There were no significant differences in the symptom prevalence rates between the two groups, after stratifying by current cigarette consumption and childhood respiratory troubles (CRT). The spirometric values were not significantly different. In both ethnic groups, the prevalence rates of wheeze, attacks of shortness of breath with wheeze (SOBWHZ), and asthma were significantly higher in those who had CRT. Among Anglos, less educated smokers had significantly higher prevalence rates of SOBWHZ and dyspnea; nonsmokers with less education had higher prevalence rates of cough, chronic cough, and dyspnea. Our results confirm the importance of CRT and lower educational level as risk factors for respiratory symptoms. Ethnicity is not associated with symptomatology or lung function impairment.

Ventricular Free-Wall Rupture after Myocardial Infarction: Treatment and Outcome—PJ Pappas, AC Cernaianu, WA Baldino, JH Cilley Jr, AJ DelRossi. Chest 1991; 99:892.

Ventricular free-wall rupture remains one of the leading causes of death after myocardial infarction (MI). With increased abilities for diagnosis and resuscitation techniques, surgical correction of free-wall myocardial defects resulting from ischemia and necrosis may become a simple modality of treatment, resulting in improvement of the survival rate. We report our experience with 4 patients with ventricular free-wall rupture after MI, with emphasis on clinical presentation, diagnosis, and surgical management.

A Multivariate Analysis of the Risk of Pulmonary Complications after Laparotomy—JC Hall, RA Tarala, JL Hall, J Mander. Chest 1991;99:923.

We evaluated the relationship between postoperative pulmonary complications (PPC) and various putative risk factors in a prospective longitudinal study of 1,000 patients undergoing abdominal surgery. Transient subclinical events were excluded by defining PPC as positive clinical findings in combination with either positive sputum microbiology, unexplained pyrexia, or positive chest roentgenographic findings. The overall incidence of PPC was 23.2% (232/1,000). Multivariate analysis identified 7 factors that were associated with PPC: ASA classification > 2, upper abdominal surgery, residual intraperitoneal sepsis, age > 59 years, body mass index (BMI) > 25, preoperative hospital stay > 4 days, and colorectal or gastroduodenal surgery (overall F score = 33.5, $p < 0.0001$). The ASA classification was the most powerful indicator of risk in both the univariant and the multivariate analyses. The combination of ASA classification > 1 and age > 59 years identified 88% (205 of 232) of the patients who developed PPC. These findings provide clinicians and clinical investigators with a simple means of identifying patients who are at high risk of PPC after abdominal surgery.

Reversible Cardiogenic Shock Due to Chest Tube Compression of the Right Ventricle—MH Kollef, DW Dothager. Chest 1991;99:976.

A 62-year-old woman developed shock immediately after the insertion of a right-sided chest tube. A chest roentgenogram showed the chest tube to be overlying the heart and possibly compressing the right ventricle. An animal model was developed to replicate this clinical situation. Using a domestic goat model, pulmonary-artery peripheral arterial catheters were inserted along with a right-sided chest tube placed to suction. A second chest tube guided by a flexible fiberoptic bronchoscope placed within its lumen was positioned between the right ventricle and the sternum of the animals. Thirteen paired measurements in three goats

More hope for infants with RDS*
More proof of effectiveness
More experience
Baby's Breath
Gypsophila paniculata

The proven efficacy and impressive safety profile of the first protein-free, synthetic lung surfactant

Exosurf® NEONATAL™
(Colfosceril Palmitate, Cetyl Alcohol, Tyloxapol) For Intratracheal Suspension

Controlled clinical trials with EXOSURF Neonatal showed "dramatic reductions" in morbidity and mortality of infants with RDS. Subsequent use under a year-long Treatment IND confirmed its efficacy and impressive safety profile. Since release for marketing in August 1990, widespread use in hospitals across the United States has further established its value in the treatment of RDS. The weight of clinical experience is in favor of EXOSURF Neonatal.

Dramatic reductions in neonatal morbidity and mortality reported in clinical trials[1-5]

Improvement in clinical outcome after EXOSURF Neonatal has been significant in infants at risk of developing RDS as well as those with established RDS. Prophylactic as well as rescue treatment with EXOSURF Neonatal has dramatically reduced morbidity and mortality in infants weighing greater than 700 grams.

SIGNIFICANT REDUCTIONS IN OVERALL MORTALITY FROM ANY CAUSE IN MIDDLE-SIZE AND LARGE INFANTS[2,5]
(Percent reductions with EXOSURF)

	Prophylactic treatment		Rescue treatment	
Age	*Single Dose*[2] 700-1100 grams (N=446)	*One vs Three Doses*[3] 700-1100 grams (N=716)	*Two Dose*[4] 700-1350 grams (N=419)	*Two Dose*[5] 1250 grams and above (N=1232)
≤10 Days	—	—	59%[§]	35%
≤28 Days	40%*	44%[‡]	52%[§]	39%
≤1 Year	44%[†]	41%[‡]	46%[§]	31%

*P=0.022 †P=0.002 ‡P<0.05. §P<0.001 P=0.039 N=Number of infants enrolled in the clinical trials.

A single prophylactic dose of EXOSURF Neonatal reduced 1-year mortality by 44%. Two additional prophylactic doses provided an additional 41% reduction in 1-year mortality.[3]

SIGNIFICANT REDUCTIONS IN MORTALITY FROM RDS IN MIDDLE-SIZE AND LARGE INFANTS[2,4,5]
(Percent reductions with EXOSURF)

	Prophylactic treatment	Rescue treatment	
	Single Dose[2] 700-1100 grams (N=446)	*Two Dose*[4] 700-1350 grams (N=419)	*Two Dose*[5] 1250 grams and above (N=1232)
Reduction in death from RDS	58%*	66%[†]	63%[‡]

*P=0.011 †P=0.007 ‡P=0.009 N=Number of infants enrolled in the clinical trials.

SIGNIFICANT REDUCTION IN CARDIOPULMONARY DESTRUCTION TO DAY 28 FOLLOWING TWO-DOSE RESCUE TREATMENT[4,5]
(Percent reductions with EXOSURF)

Birth weight	Reduction in death at 28 days or survival with broncho-pulmonary dysplasia (BPD)
700-1350[4] (N=419)	34%*
1250 and above[5] (N=1232)	43%*

*P=0.002 N=Number of infants enrolled in the clinical trials.

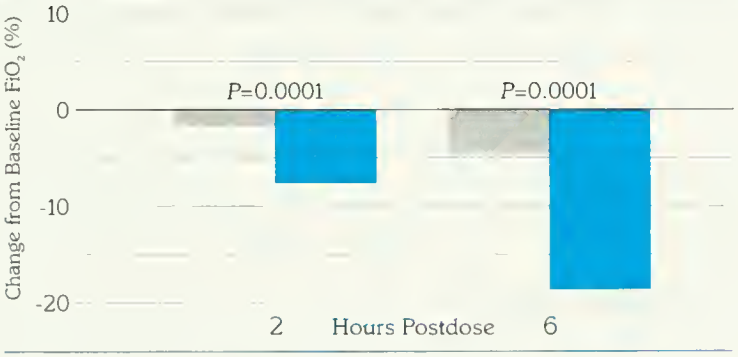
Rapid onset of action documented in rescue use[4]

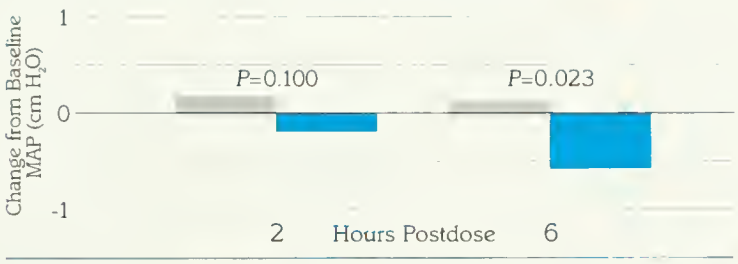
Improvements in mean FiO_2 and mean alveolar-arterial PO_2 (A-a) gradient were present by 2 hours after dosing in middle-size babies (700-1350 grams). Improvements in mean airway pressures began sometime between 2 and 6 hours in middle-size babies. These improvements persisted for at least 7 days.

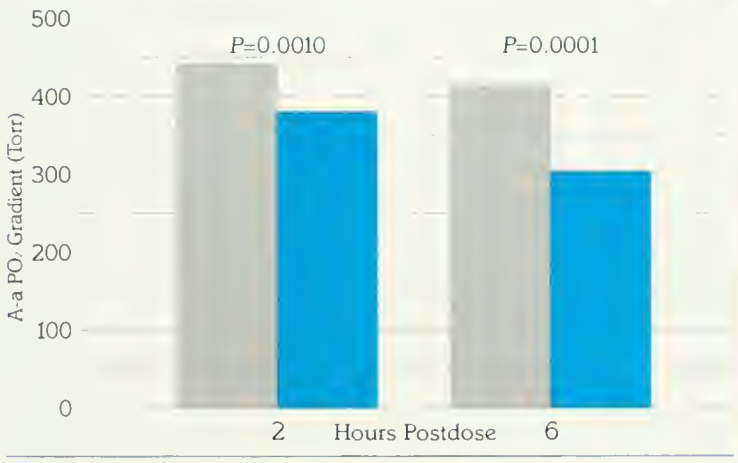
SIGNIFICANT IMPROVEMENTS IN SUPPLEMENTAL OXYGEN NEEDS AND VENTILATORY REQUIREMENTS SEEN IN MIDDLE-SIZE BABIES[4]

Air
EXOSURF Neonatal

All charts from Long[4]







Please see brief summary of full prescribing information on last pages of this advertisement.

Efficacy and impressive safety profile of EXOSURF® Neonatal™ confirmed in continued widespread use[6]

In North American controlled clinical trials, more than 2600 premature infants received EXOSURF Neonatal. Under the year-long Treatment IND, over 11,400 infants received EXOSURF Neonatal. In the six months following its release for marketing, EXOSURF Neonatal has been given to 10,000 infants in more than 750 hospitals.

There are no known infectious or immunologic risks associated with EXOSURF Neonatal use. In controlled clinical trials, adverse events were comparable to those of placebo, with the exception of apnea and pulmonary bleeding. Infants receiving EXOSURF Neonatal required less ventilatory support, possibly contributing to an increased incidence of apnea. Pulmonary bleeding occurred in 1% of control infants and 2% of treated infants in controlled trials. In the treatment IND, pulmonary bleeding was reported in 4% and mucous plugging at a rate of 3/1000. Pulmonary bleeding appears to be preventable with early diagnosis and appropriate treatment of patent ductus arteriosus.

One-year follow-up evaluated developmental outcomes[7]

Double-blind 1-year follow-up of more than 1450 infants enrolled in randomized trials showed that mental and motor scores appeared to be higher in tiny infants (<750 grams) as well as middle-size infants (750-1249 grams) who received Exosurf Neonatal.

Economic data analysis showed cost savings[8-10]

Three separate studies evaluated the economic impact of a single prophylactic dose of EXOSURF Neonatal, two-dose rescue treatment in 700- to 1350-gram infants, and two-dose rescue treatment during the neonatal period in infants weighing over 1350 grams. Results indicate that both prophylactic treatment and rescue treatment are cost-effective. Mean hospital charges were $6451 less for large infants receiving two-dose rescue treatment versus air in the first 28 days of life.[10]

As easy to use as it is effective

- **Easy to store and use** EXOSURF Neonatal may be stored at room temperature. Reconstituted suspension may be maintained refrigerated or at room temperature for up to 12 hours. Key items needed for administration are supplied in one kit.
- **Easy to administer** Each EXOSURF Neonatal dose is administered in two 2.5-mL/kg half-doses without interrupting mechanical ventilation.
- **Easy on infant** To assist the distribution of EXOSURF Neonatal in the lungs, the infant is simply turned from midline position to the right after the first half-dose, and from midline position to the left after the second half-dose.

References: 1. Bose C, Corbet A, Bose G, et al. Improved outcome at 28 days of age for very low birth weight infants treated with a single dose of a synthetic surfactant. *J Pediatr.* 1990;117:947-953. **2.** Corbet A, Bucciarelli R, Goldman S, et al. Decreased mortality in small premature infants treated at birth with a single dose of synthetic surfactant: a multi-center controlled trial. *J Pediatr.* 1991;118:277-284. **3.** Gerdes J, Cook L, Beaumont E, Corbet A, Long W. American EXOSURF Pediatric Groups I and II. Effects of three vs. one prophylactic doses of EXOSURF Neonatal in 700- to 1100-gram neonates. *Pediatr Res.* 1991;29(no. 4, pt 2):214A. Abstract. **4.** Long W, Thompson T, Sundell H, et al. Effects of two rescue doses of a synthetic surfactant on mortality rate and survival without bronchopulmonary dysplasia in 700- to 1350-gram infants with respiratory distress syndrome. *J Pediatr.* 1991;118:595-605. **5.** U.S. and Canadian EXOSURF Pediatric Study Groups. Effects of two rescue doses of EXOSURF® Pediatric in 1232 infants ≥1250 grams. *Pediatr Res.* 1990;27(no. 4, pt 2):320A. Abstract. **6.** Data on file, Burroughs Wellcome Co., 1991. **7.** Walter D, McGuinness G, Bose C, et al. Double-blind one-year follow-up in 1450 infants randomized to EXOSURF® Neonatal or air. *Pediatr Res.* 1991;29(no. 4, pt 2):270A. Abstract. **8.** Sell M, Corbet A, Gong A, et al. Economic impact of a single prophylactic dose of EXOSURF® Neonatal in 700- to 1100-gram infants. *Pediatr Res.* 1991;29(no. 4, pt 2):265A. Abstract. **9.** Mammel M, Mullett M, Derleth D, et al. Economic impact of two rescue doses of EXOSURF® Neonatal in 700-1350 gram infants. *Pediatr Res.* 1991;29(no. 4, pt 2):260A. Abstract. **10.** Schumacher R, Burchfield D, Vaughan R, et al. Economic impact of two rescue doses of EXOSURF® Neonatal in ≥1350 gram infants. *Pediatr Res.* 1991;29(no. 4, pt 2):264A. Abstract.

Please see brief summary of full prescribing information on last pages of this advertisement.

Wellcome

Copr © 1991 Burroughs Wellcome Co. All rights reserved

EX Y01228

EXOSURF® Neonatal™
(COLFOSCERIL PALMITATE, CETYL ALCOHOL, TYLOXAPOL)
For Intratracheal Suspension / 10 mL vials

PLEASE CONSULT FULL PRODUCT INFORMATION BEFORE PRESCRIBING

INDICATIONS AND USAGE: Exosurf Neonatal is indicated for

1 **Prophylactic** treatment of infants with birth weights of less than 1350 grams who are at risk of developing RDS (see PRECAUTIONS).

2 **Prophylactic** treatment of infants with birth weights greater than 1350 grams who have evidence of pulmonary immaturity, and

3 **Rescue** treatment of infants who have developed RDS

CONTRAINDICATIONS: There are no known contraindications to treatment with Exosurf Neonatal

WARNINGS: **Intratracheal Administration Only**: Exosurf Neonatal should be administered only by instillation into the trachea. **General**: The use of Exosurf Neonatal requires expert clinical care by experienced neonatologists and other clinicians who are accomplished at neonatal intubation and ventilatory management. Adequate personnel, facilities, equipment, and medications are required to optimize perinatal outcome in premature infants. Instillation of Exosurf Neonatal should be performed **only** by trained medical personnel experienced in airway and clinical management of unstable premature infants. Vigilant clinical attention should be given to all infants prior to, during, and after administration of Exosurf Neonatal. **Acute Effects**: Exosurf Neonatal can rapidly affect oxygenation and lung compliance. **Lung Compliance**: If chest expansion improves substantially after dosing, peak ventilator inspiratory pressures should be reduced immediately, without waiting for confirmation of respiratory improvement by blood gas assessment. Failure to reduce inspiratory ventilator pressures rapidly in such instances can result in lung overdistention and fatal pulmonary air leak. **Hyperoxia**: If the infant becomes pink and transcutaneous oxygen saturation is in excess of 95%, FiO_2 should be reduced in small but repeated steps (until saturation is 90 to 95%) without waiting for confirmation of elevated arterial pO_2 by blood gas assessment. Failure to reduce FiO_2 in such instances can result in hyperoxia. **Hypocarbia**: If arterial or transcutaneous CO_2 measurements are <30 torr, the ventilator rate should be reduced at once. Failure to reduce ventilator rates in such instances can result in marked hypocarbia, which is known to reduce brain blood flow. **Pulmonary Hemorrhage**: In the single study conducted in infants weighing <700 grams at birth, the incidence of pulmonary hemorrhage (10% vs 2% in the placebo group) was significantly increased in the Exosurf Neonatal group. None of the five studies involving infants with birth weights >700 grams showed a significant increase in pulmonary hemorrhage in the Exosurf Neonatal group. In a cross-study analysis of these five studies, pulmonary hemorrhage was reported for 1% (14/1420) of infants in the placebo group and 2% (27/1411) of infants in the Exosurf Neonatal group. Fatal pulmonary hemorrhage occurred in three infants: two in the Exosurf Neonatal group and one in the placebo group. Mortality from all causes among infants who developed pulmonary hemorrhage was 43% in the placebo group and 37% in the Exosurf Neonatal group. Pulmonary hemorrhage in both Exosurf Neonatal and placebo infants was more frequent in infants who were younger, smaller, male, or who had a patent ductus arteriosus. Pulmonary hemorrhage typically occurred in the first 2 days of life in both treatment groups. In more than 7700 infants in the open, uncontrolled study, pulmonary hemorrhage was reported in 4%, but fatal pulmonary hemorrhage was reported rarely (0.4%). In the controlled clinical studies, Exosurf Neonatal treated infants who received steroids more than 24 hours prior to delivery or indomethacin postnatally had a lower rate of pulmonary hemorrhage than other Exosurf Neonatal treated infants. Attention should be paid to early and aggressive diagnosis and treatment (unless contraindicated) of patent ductus arteriosus during the first 2 days of life (while the ductus arteriosus is often clinically silent). Other potentially protective measures include attempting to decrease FiO_2 preferentially over ventilator pressures during the first 24 to 48 hours after dosing, and attempting to decrease PEEP minimally for at least 48 hours after dosing. **Mucous Plugs**: Infants whose ventilation becomes markedly impaired during or shortly after dosing may have mucous plugging of the endotracheal tube, particularly if pulmonary secretions were prominent prior to drug administration. Suctioning of all infants prior to dosing may lessen the chance of mucous plugs obstructing the endotracheal tube. If endotracheal tube obstruction from such plugs is suspected, and suctioning is unsuccessful in removing the obstruction, the blocked endotracheal tube should be replaced immediately.

PRECAUTIONS

General: In the controlled clinical studies, infants known prenatally or postnatally to have major congenital anomalies, or who were suspected of having congenital infection, were excluded from entry. However, these disorders cannot be recognized early in life in all cases, and a few infants with these conditions were entered. The benefits of Exosurf Neonatal in the affected infants who received drug appeared to be similar to the benefits observed in infants without anomalies or occult infection. **Prophylactic Treatment - Infants <700 Grams**: In infants weighing 500 to 700 grams, a single prophylactic dose of Exosurf Neonatal significantly improved FiO_2 and ventilator settings, reduced pneumothorax, and reduced death from RDS, but increased pulmonary hemorrhage (see WARNINGS). Overall mortality did not differ significantly between the placebo and Exosurf Neonatal groups (see Table 1 in full product information). Data on multiple doses in infants in this weight class are not yet available. Accordingly, clinicians should carefully evaluate the potential risks and benefits of Exosurf Neonatal administration in these infants. **Rescue Treatment - Number of Doses**: A small number of infants with RDS have received more than two doses of Exosurf Neonatal as rescue treatment. Definitive data on the safety and efficacy of these additional doses are not available. **Carcinogenesis, Mutagenesis, Impairment of Fertility**: Exosurf Neonatal at concentrations up to 10,000 µg/plate was not mutagenic in the Ames Salmonella assay. Long-term studies have not been performed in animals to evaluate the carcinogenic potential of Exosurf Neonatal. The effects of Exosurf Neonatal on fertility have not been studied.

ADVERSE REACTIONS:

General: Premature birth is associated with a high incidence of morbidity and mortality. Despite significant reductions in overall mortality associated with Exosurf Neonatal, some infants who received Exosurf Neonatal developed severe complications and either survived with permanent handicaps or died.

In controlled clinical studies evaluating the safety and efficacy of Exosurf Neonatal, numerous safety assessments were made. In infants receiving Exosurf Neonatal, pulmonary hemorrhage, apnea and use of methylxanthines were increased. A number of other adverse events were significantly reduced in the Exosurf Neonatal group, particularly various forms of pulmonary air leak and use of pancuronium. Tables 3 and 4 summarize the results of the major safety evaluations from the controlled clinical studies.

Table 3 Safety Assessments[a]—Prophylactic Treatment

Number of Doses / Birth Weight Range	Single Dose 500 to 700 grams		Single Dose 700 to 1350 grams		Single Dose 700 to 1100 grams		1 vs 3 Doses 700 to 1100 grams	
Treatment Group / Number of Infants	Placebo (Air) N=108	EXOSURF N=107	Placebo (Air) N=193	EXOSURF N=192	Placebo (Air) N=222	EXOSURF N=224	EXOSURF 1 Dose N=356	EXOSURF 3 Doses N=360
	% of Infants		% of Infants		% of Infants		% of Infants	
Intraventricular Hemorrhage (IVH)								
Overall	51	57	31	27	36	36	38	35
Severe IVH	26	25	10	8	13	14	9	9
Pulmonary Air Leak (PAL)								
Overall	52	48	16	11	32	25	29	27
Pneumothorax	23	10*	5	6	19	11*	14	12
Pneumopericardium	1	4	2	0	<1	1	1	1
Pneumomediastinum	2	1	2	3	7	1**	3	2
Pulmonary Interstitial Emphysema	43	44	13	7*	26	20	23	22
Death from PAL	4	6	<1	<1	2	1	2	1
Patent Ductus Arteriosus	49	53	66	70	50	55	59	57
Necrotizing Enterocolitis	2	4	11	13	3	4	6	2*
Pulmonary Hemorrhage	2	10**	2	4	1	4	4	6
Congenital Pneumonia	4	4	2	4	2	2	1	1
Nosocomial Pneumonia	10	10	2	4	4	7	14	15
Non-Pulmonary Infections	33	35	34	39	28	29	35	34
Sepsis	30	34	30	34	23	24	30	27
Death From Sepsis	4	4	3	3	1	2	3	2
Meningitis	4	6	3	1	2	3	1	2
Other Infections	7	4	5	3	6	10	10	11
Major Anomalies	3	1	2	4	7	4	4	4

Table 3 Safety Assessments[a]—Prophylactic Treatment (Cont.)

Number of Doses / Birth Weight Range	Single Dose 500 to 700 grams		Single Dose 700 to 1350 grams		Single Dose 700 to 1100 grams		1 vs 3 Doses 700 to 1100 grams	
Treatment Group / Number of Infants	Placebo (Air) N=108	EXOSURF N=107	Placebo (Air) N=193	EXOSURF N=192	Placebo (Air) N=222	EXOSURF N=224	EXOSURF 1 Dose N=356	EXOSURF 3 Doses N=360
	% of Infants		% of Infants		% of Infants		% of Infants	
Hypotension	70	77	52	47	59	62	54	50
Hyperbilirubinemia	22	21	63	61	27	31	20	21
Exchange Transfusion	4	3	1	2	2	2	3	1
Thrombocytopenia[b]	21	25	not available		9	8	12	10
Persistent Fetal Circulation	0	1	1	1	0	2*	1	<1
Seizures	11	8	2	2	11	9	6	5
Apnea	34	33	76	73	55	65*	62	68
Drug Therapy								
Antibiotics	96	99	98	96	98	99	>99	99
Diuretics	55	60	39	37	59	63	64	65
Anticonvulsants	14	18	23	24	20	16	9	8
Inotropes	46	40	20	20	26	20	28	27
Sedatives	62	71	65	64	63	57	52	52
Pancuronium	19	11	22	14*	19	13*	15	11
Methylxanthines	38	43	77	77	61	72*	75	82*

[a] All parameters were examined with "as-treated" analyses. * p<0.05; ** p<0.01
[b] Thrombocytopenia requiring platelet transfusion

Table 4 Safety Assessments[a]—Rescue Treatment

Number of Doses / Birth Weight Range	Two Doses 700 to 1350 grams		Two Doses 1250 grams and above	
Treatment Group / Number of Infants	Placebo (Air) N=213	EXOSURF N=206	Placebo (Air) N=622	EXOSURF N=615
	% of Infants		% of Infants	
Intraventricular Hemorrhage (IVH)				
Overall	48	52	23	18*
Severe IVH	13	9	5	4
Pulmonary Air Leak (PAL)				
Overall	54	34***	30	18***
Pneumothorax	29	20*	20	10***
Pneumopericardium	4	1	1	2
Pneumomediastinum	8	4	5	2**
Pulmonary Interstitial Emphysema	48	25***	24	13***
Death from PAL	7	3	<1	1
Patent Ductus Arteriosus	66	57	54	45*
Necrotizing Enterocolitis	3	3	1	2
Pulmonary Hemorrhage	3	1	<1	1
Congenital Pneumonia	2	3	2	2
Nosocomial Pneumonia	5	7	2	2
Non-Pulmonary Infections	19	22	13	13
Sepsis	15	17	8	8
Death From Sepsis	<1	<1	1	<1
Meningitis	1	<1	1	<1*
Other Infections	5	8	5	6
Major Anomalies	3	3	4	4
Hypotension	62	57	50	39**
Hyperbilirubinemia	17	19	12	10
Exchange Transfusion	3	4	1	2
Thrombocytopenia[b]	10	11	4	<1**
Persistent Fetal Circulation	1	1	6	2**
Seizures	10	10	6	3*
Apnea	48	65**	37	44*
Drug Therapy				
Antibiotics	100	99	98	98
Diuretics	60	65	45	34***
Anticonvulsants	17	17	10	5**
Inotropes	36	31	27	16***
Sedatives	72	68	76	64***
Pancuronium	34	17**	33	15***
Methylxanthines	62	74**	49	53

[a] All parameters were examined with "as-treated" analyses. * p<0.05; ** p<0.01; *** p<0.001
[b] Thrombocytopenia requiring platelet transfusion

Pulmonary Hemorrhage: See WARNINGS. **Abnormal Laboratory Values**: Abnormal laboratory values are common in critically ill, mechanically ventilated, premature infants. A higher incidence of abnormal laboratory values in the Exosurf Neonatal group was not reported. **Events During Dosing**: Data on events during dosing are available from more than 8800 infants in the open, uncontrolled clinical study (Table 5).

Table 5 Events During Dosing in the Open, Uncontrolled Study[a]

Treatment Type / Number of Infants	Prophylactic Treatment N=1127	Rescue Treatment N=7711
	% of Infants	% of Infants
Reflux of Exosurf	20	31
Drop in O_2 saturation (≥ 20%)	6	22
Rise in O_2 saturation (≥ 10%)	5	6
Drop in transcutaneous pO_2 (≥ 20 mm Hg)	1	8
Rise in transcutaneous pO_2 (≥ 20 mm Hg)	2	5
Drop in transcutaneous pCO_2 (≥ 20 mm Hg)	<1	1
Rise in transcutaneous pCO_2 (≥ 20 mm Hg)	1	3
Bradycardia (<60 beats/min)	1	3
Tachycardia (>200 beats/min)	<1	<1
Gagging	1	5
Mucous Plugs	<1	<1

[a] Infants may have experienced more than one event. Investigators were prohibited from adjusting FiO_2 and/or ventilator settings during dosing unless significant clinical deterioration occurred.

Reflux: Reflux of Exosurf Neonatal into the endotracheal tube during dosing has been observed and may be associated with rapid drug administration. If reflux occurs, drug administration should be halted and, if necessary, peak inspiratory pressure on the ventilator should be increased by 4 to 5 cm H_2O until the endotracheal tube clears. ***>20% Drop in Transcutaneous Oxygen Saturation***: If transcutaneous oxygen saturation declines during dosing, drug administration should be halted and, if necessary, peak inspiratory pressure on the ventilator should be increased by 4 to 5 cm H_2O for 1 to 2 minutes. In addition, increases of FiO_2 may be required for 1 to 2 minutes. ***Mucous Plugs***: See WARNINGS.

DOSAGE AND ADMINISTRATION: See full product information.

BURROUGHS WELLCOME CO., Research Triangle Park, NC 27709
Copr. © 1991 Burroughs Wellcome Co. All rights reserved
Printed in U.S.A.
EX-Y01228

Wellcome

Circle 115 on reader service card

Efficacy and impressive safety profile of EXOSURF® Neonatal™ confirmed in continued widespread use[6]

In North American controlled clinical trials, more than 2600 premature infants received EXOSURF Neonatal. Under the year-long Treatment IND, over 11,400 infants received EXOSURF Neonatal. In the six months following its release for marketing, EXOSURF Neonatal has been given to 10,000 infants in more than 750 hospitals.

There are no known infectious or immunologic risks associated with EXOSURF Neonatal use. In controlled clinical trials, adverse events were comparable to those of placebo, with the exception of apnea and pulmonary bleeding. Infants receiving EXOSURF Neonatal required less ventilatory support, possibly contributing to an increased incidence of apnea. Pulmonary bleeding occurred in 1% of control infants and 2% of treated infants in controlled trials. In the treatment IND, pulmonary bleeding was reported in 4% and mucous plugging at a rate of 3/1000. Pulmonary bleeding appears to be preventable with early diagnosis and appropriate treatment of patent ductus arteriosus.

One-year follow-up evaluated developmental outcomes[7]

Double-blind 1-year follow-up of more than 1450 infants enrolled in randomized trials showed that mental and motor scores appeared to be higher in tiny infants (<750 grams) as well as middle-size infants (750-1249 grams) who received Exosurf Neonatal.

Economic data analysis showed cost savings[8-10]

Three separate studies evaluated the economic impact of a single prophylactic dose of EXOSURF Neonatal, two-dose rescue treatment in 700- to 1350-gram infants, and two-dose rescue treatment during the neonatal period in infants weighing over 1350 grams. Results indicate that both prophylactic treatment and rescue treatment are cost-effective. Mean hospital charges were $6451 less for large infants receiving two-dose rescue treatment versus air in the first 28 days of life.[10]

As easy to use as it is effective

- **Easy to store and use** EXOSURF Neonatal may be stored at room temperature. Reconstituted suspension may be maintained refrigerated or at room temperature for up to 12 hours. Key items needed for administration are supplied in one kit.
- **Easy to administer** Each EXOSURF Neonatal dose is administered in two 2.5-mL/kg half-doses without interrupting mechanical ventilation.
- **Easy on infant** To assist the distribution of EXOSURF Neonatal in the lungs, the infant is simply turned from midline position to the right after the first half-dose, and from midline position to the left after the second half-dose.

References: 1. Bose C, Corbet A, Bose G, et al. Improved outcome at 28 days of age for very low birth weight infants treated with a single dose of a synthetic surfactant. *J Pediatr.* 1990;117:947-953. **2.** Corbet A, Bucciarelli R, Goldman S, et al. Decreased mortality in small premature infants treated at birth with a single dose of synthetic surfactant: a multi-center controlled trial. *J Pediatr.* 1991;118:277-284. **3.** Gerdes J, Cook J, Beaumont E, Corbet A, Long W. American EXOSURF Pediatric Groups I and II. Effects of three vs. one prophylactic doses of EXOSURF Neonatal in 700- to 1100-gram neonates. *Pediatr Res.* 1991;29(no. 4, pt 2):214A. Abstract. **4.** Long W, Thompson T, Sundell H, et al. Effects of two rescue doses of a synthetic surfactant on mortality rate and survival without bronchopulmonary dysplasia in 700- to 1350-gram infants with respiratory distress syndrome. *J Pediatr.* 1991;118:595-605. **5.** U.S. and Canadian EXOSURF Pediatric Study Groups. Effects of two rescue doses of EXOSURF® Pediatric in 1232 infants ≥1250 grams. *Pediatr Res.* 1990;27(no. 4, pt 2):320A. Abstract. **6.** Data on file, Burroughs Wellcome Co., 1991. **7.** Walter D, McGuinness G, Bose C, et al. Double-blind one-year follow-up in 1450 infants randomized to EXOSURF® Neonatal or air. *Pediatr Res.* 1991;29(no. 4, pt 2):270A. Abstract. **8.** Seli M, Corbet A, Gong A, et al. Economic impact of a single prophylactic dose of EXOSURF® Neonatal in 700- to 1100-gram infants. *Pediatr Res.* 1991;29(no. 4 pt 2):265A. Abstract. **9.** Mammel M, Mullett M, Derleth D, et al. Economic impact of two rescue doses of EXOSURF® Neonatal in 700-1350 gram infants. *Pediatr Res.* 1991;29(no. 4, pt 2):266A. Abstract. **10.** Schumacher R, Burchfield D, Vaughan R, et al. Economic impact of two rescue doses of EXOSURF® Neonatal in ≥1350 gram infants. *Pediatr Res.* 1991;29(no. 4, pt 2):264A. Abstract.

Please see brief summary of full prescribing information on last pages of this advertisement.

Wellcome

Copyright © 1991 Burroughs Wellcome Co. All rights reserved.

EX-Y01225

EXOSURF® Neonatal™
(COLFOSCERIL PALMITATE, CETYL ALCOHOL, TYLOXAPOL)
For Intratracheal Suspension / 10 mL vials

PLEASE CONSULT FULL PRODUCT INFORMATION BEFORE PRESCRIBING

INDICATIONS AND USAGE. Exosurf Neonatal is indicated for:

1. **Prophylactic** treatment of infants with birth weights of less than 1350 grams who are at risk of developing RDS (see PRECAUTIONS)
2. **Prophylactic** treatment of infants with birth weights greater than 1350 grams who have evidence of pulmonary immaturity, and
3. **Rescue** treatment of infants who have developed RDS

CONTRAINDICATIONS. There are no known contraindications to treatment with Exosurf Neonatal.

WARNINGS: Intratracheal Administration Only. Exosurf Neonatal should be administered only by instillation into the trachea. **General.** The use of Exosurf Neonatal requires expert clinical care by experienced neonatologists and other clinicians who are accomplished at neonatal intubation and ventilatory management. Adequate personnel, facilities, equipment, and medications are required to optimize perinatal outcome in premature infants. Instillation of Exosurf Neonatal should be performed **only** by trained medical personnel experienced in airway and clinical management of unstable premature infants. Vigilant clinical attention should be given to all infants prior to, during, and after administration of Exosurf Neonatal. **Acute Effects.** Exosurf Neonatal can rapidly affect oxygenation and lung compliance. **Lung Compliance.** If chest expansion improves substantially after dosing, peak ventilator inspiratory pressures should be reduced immediately, without waiting for confirmation of respiratory improvement by blood gas assessment. Failure to reduce inspiratory ventilator pressures rapidly in such instances can result in lung overdistention and fatal pulmonary air leak. **Hyperoxia.** If the infant becomes pink and transcutaneous oxygen saturation is in excess of 95%, FiO_2 should be reduced in small but repeated steps until saturation is 90 to 95%, without waiting for confirmation of elevated arterial pO_2 by blood gas assessment. Failure to reduce FiO_2 in such instances can result in hyperoxia. **Hypocarbia.** If arterial or transcutaneous CO_2 measurements are <30 torr, the ventilator rate should be reduced at once. Failure to reduce ventilator rates in such instances can result in marked hypocarbia, which is known to reduce brain blood flow. **Pulmonary Hemorrhage.** In the single study conducted in infants weighing <700 grams at birth, the incidence of pulmonary hemorrhage (10% vs 2% in the placebo group) was significantly increased in the Exosurf Neonatal group. None of the five studies involving infants with birth weights >700 grams showed a significant increase in pulmonary hemorrhage in the Exosurf Neonatal group. In a cross-study analysis of these five studies, pulmonary hemorrhage was reported for 3% (34/1420) of infants in the placebo group and 2% (27/1411) of infants in the Exosurf Neonatal group. Fatal pulmonary hemorrhage occurred in three infants, two in the Exosurf Neonatal group and one in the placebo group. Mortality from all causes among infants who developed pulmonary hemorrhage was 43% in the placebo group and 37% in the Exosurf Neonatal group. Pulmonary hemorrhage in both Exosurf Neonatal and placebo infants was more frequent in infants who were younger, smaller, male, or who had a patent ductus arteriosus. Pulmonary hemorrhage typically occurred in the first 2 days of life in both treatment groups. In more than 7700 infants in the open, uncontrolled study, pulmonary hemorrhage was reported in 4% but fatal pulmonary hemorrhage was reported rarely (0.4%) in the controlled clinical studies. Exosurf Neonatal treated infants who received steroids more than 24 hours prior to delivery or indomethacin postnatally had a lower rate of pulmonary hemorrhage than other Exosurf Neonatal treated infants. Attention should be paid to early and aggressive diagnosis and treatment (unless contraindicated) of patent ductus arteriosus during the first 2 days of life, while the ductus arteriosus is often clinically silent. Other potentially protective measures include attempting to decrease FiO_2 preferentially over ventilator pressures during the first 24 to 48 hours after dosing, and attempting to decrease PEEP minimally for at least 48 hours after dosing. **Mucous Plugs.** Infants whose ventilation becomes markedly impaired during or shortly after dosing may have mucous plugging of the endotracheal tube, particularly if pulmonary secretions were prominent prior to drug administration. Suctioning of all infants prior to dosing may lessen the chance of mucous plugs obstructing the endotracheal tube. If endotracheal tube obstruction from such plugs is suspected, and suctioning is unsuccessful in removing the obstruction, the blocked endotracheal tube should be replaced immediately.

PRECAUTIONS

General: In the controlled clinical studies, infants known prenatally or postnatally to have major congenital anomalies or who were suspected of having congenital infection were excluded from entry. However, these disorders cannot be recognized early in life in all cases, and a few infants with these conditions were entered. The benefits of Exosurf Neonatal in the affected infants who received drug appeared to be similar to the benefits observed in infants without anomalies or occult infection. **Prophylactic Treatment–Infants <700 Grams.** In infants weighing 500 to 700 grams, a single prophylactic dose of Exosurf Neonatal significantly improved FiO_2 and ventilator settings, reduced pneumothorax, and reduced death from RDS, but increased pulmonary hemorrhage (see WARNINGS). Overall mortality did not differ significantly between the placebo and Exosurf Neonatal groups (see Table 1 in full product information). Data on multiple doses in infants in this weight class are not yet available. Accordingly, clinicians should carefully evaluate the potential risks and benefits of Exosurf Neonatal administration in these infants. **Rescue Treatment–Number of Doses.** A small number of infants with RDS have received more than two doses of Exosurf Neonatal as rescue treatment. Definitive data on the safety and efficacy of these additional doses are not available. **Carcinogenesis, Mutagenesis, Impairment of Fertility.** Exosurf Neonatal at concentrations up to 10 000 µg/plate was not mutagenic in the Ames Salmonella assay. Long-term studies have not been performed in animals to evaluate the carcinogenic potential of Exosurf Neonatal. The effects of Exosurf Neonatal on fertility have not been studied.

ADVERSE REACTIONS

General: Premature birth is associated with a high incidence of morbidity and mortality. Despite significant reductions in overall mortality associated with Exosurf Neonatal, some infants who received Exosurf Neonatal developed severe complications and either survived with permanent handicaps or died.

In controlled clinical studies evaluating the safety and efficacy of Exosurf Neonatal, numerous safety assessments were made. In infants receiving Exosurf Neonatal, pulmonary hemorrhage, apnea and use of methylxanthines were increased. A number of other adverse events were significantly reduced in the Exosurf Neonatal group, particularly various forms of pulmonary air leak and use of pancuronium. Tables 3 and 4 summarize the results of the major safety evaluations from the controlled clinical studies.

Table 3 Safety Assessments[a]—Prophylactic Treatment

Number of Doses / Birth Weight Range	Single Dose 500 to 700 grams		Single Dose 700 to 1350 grams		Single Dose 700 to 1100 grams		* vs 3 Doses 700 to 1100 grams	
Treatment Group / Number of Infants	Placebo Air N = 108	EXOSURF N = 107	Placebo Air N = 193	EXOSURF N = 192	Placebo Air N = 222	EXOSURF N = 224	EXOSURF * Dose N = 356	EXOSURF 3 Doses N = 360
	% of Infants		% of Infants		% of Infants		% of Infants	
Intraventricular Hemorrhage (IVH)								
Overall	51	57	31	37	36	36	38	35
Severe IVH	26	25	10	8	13	12	9	9
Pulmonary Air Leak (PAL)								
Overall	52	48	16	11	32	25	26	22
Pneumothorax	23	16*	5	6	19	11*	14	10
Pneumopericardium	1	4	2	0	<1	1	1	1
Pneumomediastinum	2	1	2	3	1	1**	3	2
Pulmonary Interstitial Emphysema	43	44	13	7*	35	20	23	22
Death from PAL	4	6	<1	<1	2	1	2	1
Patent Ductus Arteriosus	49	53	66	70	50	55	59	57
Necrotizing Enterocolitis	2	4	11	13	3	4	6	2*
Pulmonary Hemorrhage	2	10**	2	4	1	4	4	6
Congenital Pneumonia	4	4	2	4	2	2	1	1
Nosocomial Pneumonia	10	10	2	4	4	5	4	6
Non-Pulmonary Infections	33	35	34	39	25	29	32	34
Sepsis	30	34	30	34	23	24	30	27
Death From Sepsis	4	4	3	3	1	2	3	2
Meningitis	4	6	3	1	2	3	1	2
Other Infections	2	4	5	3	5	10	10	7
Major Anomalies	3	1	2	4	7	4	4	4
Hypotension	28	27	27	27	55	52	54	50
Hyperbilirubinemia	22	21	53	61*	27	34*	29	27
Exchange Transfusion	4	3	1	2	2	2	3	1
Thrombocytopenia[b]	21	25	not available		9	13	12	10
Persistent Fetal Circulation	1	1	1	1	3	7*	1	<1
Seizures	1	3	2	2	1	3	5	5
Apnea	34	33	76	73	55	62*	62	68
Drug Therapy								
Antibiotics	96	99	96	96	98	99	>99	99
Diuretics	56	60	39	37	50	63*	54	55
Anticonvulsants	14	18	23	24	20	16	21	19
Inotropes	45	40	20	20	26	20	22	21
Sedatives	52	51	55	54	53	57	53	52
Pancuronium	16	11	22	12*	16	13*	11	11
Methylxanthines	38	43	77	71	61	72*	61	62*

[a] All parameters were examined with as-treated analyses. * p<0.05, ** p<0.01

[b] Thrombocytopenia requiring platelet transfusion

Table 3 Safety Assessments[a]—Prophylactic Treatment (Cont.)

Table 4 Safety Assessments[a]—Rescue Treatment

Number of Doses / Birth Weight Range	Two Doses 700 to 1350 grams		Two Doses ≥1250 grams and above	
Treatment Group / Number of Infants	Placebo (Air) N = 213	EXOSURF N = 206	Placebo (Air) N = 622	EXOSURF N = 615
	% of Infants		% of Infants	
Intraventricular Hemorrhage (IVH)				
Overall	48	52	23	15*
Severe IVH	13	9	5	4
Pulmonary Air Leak (PAL)				
Overall	34	34***	30	15***
Pneumothorax	29	20*	20	10***
Pneumopericardium	4	1	1	2
Pneumomediastinum	6	4	2	2**
Pulmonary Interstitial Emphysema	28	25***	24	13***
Death from PAL	3	1	1	1
Patent Ductus Arteriosus	56	57	54	46*
Necrotizing Enterocolitis	3	3	2	2
Pulmonary Hemorrhage	1	1	<1	1
Congenital Pneumonia	2	3	2	2
Nosocomial Pneumonia	2	3	2	2
Non-Pulmonary Infections	22	22	13	13
Sepsis	17	17	9	9
Death From Sepsis	<1	1	<1	<1
Meningitis	1	<1	1	<1*
Other Infections	5	8	5	6
Major Anomalies	3	3	4	4
Hypotension	52	51	50	39**
Hyperbilirubinemia	11	19	12	10
Exchange Transfusion	3	4	1	2
Thrombocytopenia[b]	10	11	4	<1***
Persistent Fetal Circulation	1	1	3	2**
Seizures	10	10	3	3*
Apnea	46	55**	34	42*
Drug Therapy				
Antibiotics	100	99	98	98
Diuretics	60	65	45	34***
Anticonvulsants	11	17	10	9**
Inotropes	36	31	27	18***
Sedatives	72	68	76	74***
Pancuronium	34	47**	33	18***
Methylxanthines	52	74**	49	53

[a] All parameters were examined with as-treated analyses. * p<0.05, ** p<0.01, *** p<0.001

[b] Thrombocytopenia requiring platelet transfusion

Pulmonary Hemorrhage. See WARNINGS. **Abnormal Laboratory Values.** Abnormal laboratory values are common in critically ill, mechanically-ventilated, premature infants. A higher incidence of abnormal laboratory values in the Exosurf Neonatal group was not reported. **Events During Dosing.** Data on events during dosing are available from more than 8600 infants in the open, uncontrolled clinical study (Table 5).

Table 5 Events During Dosing in the Open, Uncontrolled Study[a]

Treatment Type / Number of Infants	Prophylactic Treatment N = 1127	Rescue Treatment N = 7714
	% of Infants	% of Infants
Reflux of Exosurf	20	31
Drop in O_2 saturation ≥ 20%[b]	5	22
Rise in O_2 saturation ≥ 10%[b]	6	6
Drop in transcutaneous pO_2 ≥ 20 mm Hg	1	3
Rise in transcutaneous pO_2 ≥ 20 mm Hg	2	5
Drop in transcutaneous pCO_2 ≥ 20 mm Hg	<1	1
Rise in transcutaneous pCO_2 ≥ 20 mm Hg	1	3
Bradycardia <60 beats/min	1	3
Tachycardia >200 beats/min	<1	<1
Gagging	1	5
Mucous Plugs	<1	<1

[a] Infants may have experienced more than one event.

[b] Investigators were prohibited from adjusting FiO_2 and/or ventilator settings during dosing unless significant clinical deterioration occurred.

Reflux. Reflux of Exosurf Neonatal into the endotracheal tube during dosing has been observed and may be associated with rapid drug administration. If reflux occurs, drug administration should be halted and, if necessary, peak inspiratory pressure on the ventilator should be increased by 4 to 5 cm H_2O until the endotracheal tube clears. ***>20% Drop in Transcutaneous Oxygen Saturation.*** If transcutaneous oxygen saturation declines during dosing, drug administration should be halted and, if necessary, peak inspiratory pressure on the ventilator should be increased by 4 to 5 cm H_2O for 1 to 2 minutes. In addition, increases of FiO_2 may be required for 1 to 2 minutes. ***Mucous Plugs.*** See WARNINGS.

DOSAGE AND ADMINISTRATION. See full product information.

BURROUGHS WELLCOME CO., Research Triangle Park, NC 27709
Copyright ©1999 Burroughs Wellcome Co. All rights reserved.
Printed in U.S.A. EX-Y0122S

Wellcome

Circle 115 on reader service card

(average of 4.3 measurements per animal) of cardiac output, heart rate, and mean arterial blood pressure were made at baseline and after chest tube placement over the right ventricle. The data were analyzed using a paired *t* test statistic. Compared with baseline measurements, there was a significant decrease in cardiac output ($p < 0.0001$) and mean arterial pressure ($p < 0.0001$) as well as an increase in heart rate ($p = 0.0056$) after placement of the chest tube across the right ventricle. We conclude that a misplaced chest tube compressing the right ventricle can impede cardiac output and lead to a low cardiac output state. Physicians inserting chest tubes in patients should be aware of this potential complication as it is easily treated by withdrawal of the chest tube.

Closure of a Bronchopleural Fistula with Bronchoscopic Instillation of Tetracycline—WR Martin, AD Siefkin, R Allen. Chest 1991;99: 1040.

Persistent bronchopleural fistulas (BPF) due to infection, trauma, or thoracic surgical procedures are often difficult to manage. We report a patient with fulminant *Staphylococcus aureus* pneumonia complicated by chronic BPF formation that prevented weaning from mechanical ventilation due to severe air leak. Fistula closure was obtained by instillation of tetracycline into the fistula via a fiberoptic bronchoscope using a balloon catheter and blood clot occlusion technique. This closed the BPF and allowed successful weaning from mechanical ventilation.

Reversible Brain Death: A Manifestation of Amitriptyline Overdose—KL Yang, DR Dantzker. Chest 1991;99:1037.

Tricyclic antidepressants are known to cause central nervous system depression. However, a generalized depression of brain-stem functions is rarely reported. We report a patient in deep coma with complete absence of brain-stem reflexes after she had taken a large quantity of amitriptyline. With continuous supportive treatment, she eventually regained all neurologic function and made a full recovery.

PEEP and "Reverse Mismatch:" A Case Where Less PEEP Is Best—FH Hawker, PJ Torzillo, AE Southee. Chest 1991;99:1034.

A $\dot{V}/\dot{Q}$ lung scan was obtained in a patient with lower left lobe (LLL) collapse who was receiving IPPV and PEEP. This revealed absent ventilation and hyperperfusion to the collapsed lobe. After a reduction in PEEP from 12 to 5 cm H_2O, a repeat $\dot{V}/\dot{Q}$ scan showed a more even distribution of pulmonary perfusion. Arterial hypoxemia improved.

Pneumatic Chest-Wall Compression: A Cause of Respiratory Failure from Massive Subcutaneous Emphysema—SE Eveloff, WE Donat, R Aisenberg, SS Braman. Chest 1991;99:1021.

Subcutaneous emphysema rarely causes significant adverse clinical consequences. Two patients had development of massive subcutaneous emphysema during positive-pressure ventilation that resulted in chest-wall compression and respiratory failure. Drainage of the subcutaneous air produced dramatic improvement. Subcutaneous emphysema is potentially fatal in ventilated patients. Specific decompression of subcutaneous tissues is indicated in such extreme cases.

Dysphagia as a Manifestation of Occult Hypoxemia: The Role of Oximetry during Meal Times—KR Chapman, AS Rebuck. Chest 1991;99: 1030.

A 25-year-old woman with severe kyphoscoliosis reported a 6-month history of increasing dysphagia to both liquids and solids. A barium swallow and esophageal motility studies showed no significant gastrointestinal abnormalities. Trials of antispasmodic agents were unsuccessful in relieving her symptoms. Pulmonary function tests showed a severe restrictive ventilatory defect (vital capacity = 0.67 L) with adequate oxygenation and alveolar ventilation as reflected by arterial blood gas testing during quiet wakefulness. However, continuous noninvasive oximetry demonstrated desaturation to 85% while eating. These transient episodes of desaturation were abolished by the administration of supplemental oxygen delivered by nasal prongs. Following the prescription of supplemental oxygen, dysphagia resolved immediately, with weight gain following over several weeks. We conclude that dysphagia may be a presenting feature of hypoxemia. This case report draws attention to the usefulness of continuous noninvasive monitoring of oxygenation and the clinical importance of at least some transient hypoxemic events.

Technetium ^{99m} Radiolabeling of Aerosolized Drug Particles from Metered Dose Inhalers—C Aug, RJ Perry, GC Smaldone. J Aerosol Med 1991;4:127.

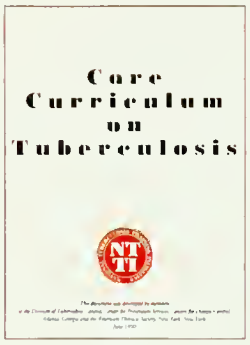
To assess mechanisms of bronchodilation and effectiveness of metered dose inhalers, it may be useful to determine sites of drug deposition in the lung. To establish suitable test aerosols, two brands of metered dose inhalers containing bronchodilator (Brethaire, Proventil) were radiolabeled with technetium (^{99m}Tc) and tested to determine if the distribution of radioisotope in the aerosol was representative of the distribution of agonist activity. Cascade impaction was used to determine the particle

size distribution of the radioisotope and drug aerosols by assaying each stage of the cascade using scintillation and high performance liquid chromatography (HPLC) techniques. Possible influences of the radiolabeling method and delivery techniques on the particle distribution were assessed by analyzing distributions from nonradiolabeled inhalers using HPLC. For these drugs, there was an excellent correlation between the distribution of radioactivity and the drug within the captured aerosol (Brethaire, r = 0.994, Proventil, r = 0.998; 20-200 consecutive puffs). Distributions were close to log-normal and differences in mass median aerodynamic diameter (MMAD) between the radioisotope and agonist activities were not significant (Brethaire, MMAD + σ g, radiolabel vs drug = 4.7 ± 2.1 μm, vs 4.4 ± 1.7 μm, and Proventil, 2.5 ± 2.1 μm, vs 2.4 ± 2.0 μm. Non-labeled inhalers produced similar drug distributions (Brethaire 4.2 ± 1.8 μm, and Proventil 2.0 ± 1.9 μm). Pausing between actuations resulted in slightly smaller distributions (Brethaire, 3.6 ± 1.8 μm, Proventil 1.8 ± 1.8 μm, 20 puffs-60 pauses) but the differences were not significant. In addition, to search for multimodal distributions and assess the accuracy of the MMAD measurement via our cascade impactor (Delron), we also measured the distribution of the mass of material within the aerosols using a weight-sensitive cascade (California Measurements). Using the latter device (1 puff), the mass distributions of both aerosols were similar to the values obtained from the puffs with pauses (Brethaire 3.8 ± 2.3 μm, Proventil 1.4 ± 2.2 μm). Multimodal distributions were not found. By all assessments, the distributions were nearly log-normal with drug activity well described by the radiolabel.

A Single-Blind Study of Combined Pulse Oximetry and Capnography in Children—CJ Cote, N Rolf, LMP Liu, NG Goudsouzian, JF Ryan, A Zaslavsky, et al. Anesthesiology 1991; 74:980.

This single-blind study examined four levels of monitoring in 402 pediatric cases. Patients were randomly assigned to one of four groups: (1) oximeter and capnograph, (2) only oximeter, (3) only capnograph, or (4)

THE
CDC



Wants You To Know...

- *In the United States, the 30 year decline in TB cases has ended.*
- *An estimated 10 to 15 million persons in the United States are infected with the TB bacillus.*
- *The potential airborne transmission of TB and multi-drug resistant TB places healthcare workers at risk.*
- *All potients with HIV infection and undiognosed pulmonary disease should be suspected of having TB and appropriate precautions to prevent airborne transmission should be taken.*

We Want You To Know About...

ISOL AIDE™
Isolation Rooms and Chambers
CALL 1-800-ISOLATE

© Component Systems, Inc., 1991
Patent Pending

Circle 118 on reader service card

neither oximeter nor capnograph data available to the anesthesia team. An anesthesiologist, not involved in patient care, observed all cases and continuously recorded hemoglobin oxygen saturation (S_{pO_2}), ECG, expired CO_2, and the oximeter plethysmographic output. Mean age, weight, ASA physical status, airway management (mask or endotracheal tube), and anesthetic techhnique were similar in each group. Two-hundred-sixty problems were documented in 153 patients. Fifty-nine events in 43 patients resulted in "major" desaturation ($S_{pO_2} \leq 85\%$ for $\geq$ 30 seconds). Fifteen "major" capnograph events (esophageal intubation, disconnection, accidental extubation, or obstructed endotracheal tube) were observed in 11 patients; 8 of these also developed varying degrees of desaturation. One-hundred thirty "minor" desaturation events ($S_{pO_2} \leq 95\%$ for $\geq$ 60 seconds) and 79 "minor" capnograph events (hypercarbia or hypocarbia) were observed. A number of problems fulfilled criteria in multiple categories. Infants $\leq$ 6 months of age had the highest incidence of major desaturation events (18 of 65 [27%]) compared to toddlers 7-24 months of age or children $\geq$ 24 months of age ($p < 0.001$). Blinding the oximeter data increased the number of patients (12 vs 31) experiencing major desaturation events ($p = 0.003$); blinding the capnograph data altered neither the frequency of desaturation events nor the incidence of major capnograph events. Blinding the capnograph data increased the number of patients with minor capnograph events (22 vs 47; $p = 0.0026$). More patients experienced multiple problems when neither capnograph nor oximeter data were available compared to when both were available (23 vs 11; $p = 0.04$). We conclude: (1) The pulse oximeter is far superior to either the capnograph or clinical judgment in providing the earliest warning of desaturation events. (2) Capnography can provide an early warning to potentially life-threatening problems, but such problems often result in desaturation. (3) Capnography reduces the incidence of hypercarbia and hypocarbia. (4) Infants $\leq$ 6 months of age are at greatest risk for major desaturation and major capnograph events. (5) The number of problems observed can be significantly reduced when both monitors are used.

Comparison of Three Methods for Measuring Respiratory Mechanics in Ventilated Children—M Seear, D Wensley, H Werner. Pediatr Pulmonol 1991;10:291.

Continuous measurements of airway pressure, gas flow, and tidal volume were made in 22 mechanically ventilated children, both during steady-state conditions and following airway occlusion at end-inflation. For each child, three methods of analyzing the stored data were used to generate values of respiratory system compliance and resistance: (1) end-inspiratory hold technique (Bone, Respir Care 1983;28:597; Rossi, et al. Am Rev Respir Dis 1985;131: 672); (2) constant flow technique (Rossi, et al. J Appl Physiol 1985;58: 1849; Suratt, et al. J Appl Physiol 1980;49:1116); and (3) multiple linear regression (Roy, et al. Comput Biomed Res 1974;7:21; Bhutani, et al. Pediatr Pulmonol 1988;4:150). In the absence of an accepted standard, we used the inspiratory hold technique as a reference. All methods gave comparable values for respiratory mechanics over a wide clinical range. However, multiple linear regression was the most convenient of the three: It can be automated and continuously displayed, there is no subjective input, values are taken throughout the respiratory cycle, and it is completely noninvasive. We also found that respiratory system resistance was largely a measure of endotracheal-tube resistance and that respiratory compliance is a more sensitive monitor of lung function in intubated children.

Effect of Vascular Puncture on Blood Gases in the Newborn—EH Kim, RS Cohen, P Ramachandran. Pediatr Pulmonol 1991;10:287.

Continuous monitoring methods have shown changes of oxygenation in neonates during various procedures. However, actual changes in blood gases during vascular punctures have not been reported. We studied the effect of vascular puncture on arterial blood gases during routine venipuncture in 17 neonates who had indwelling arterial catheters. Arterial blood gases were analyzed before, during, and following recovery from venipuncture. Ventilator settings were not changed during the study, though oxygen concentration (F_{IO_2}) was adjusted as indicated by continuous P_{O_2} or saturation monitors. During venipuncture, there was a significant fall in P_{aCO_2} from 38 $\pm$ 5 to 32 $\pm$ 7 torr ($p < 0.0001$) and in P_{aO_2} from 75 $\pm$ 21 to 58 $\pm$ 23 torr ($p < 0.0001$). Following venipuncture, both values returned to baseline. The results of this study imply that blood gases obtained by intermittent arterial sticks may provide data that do not accurately reflect the neonates' respiratory status.

Predicted Values for Lung Diffusing Capacity in Healthy Children—SZ Nasr, P Amato, RW Wilmott. Pediatr Pulmonol 1991;10: 267.

Lung diffusing capacity was measured in 92 healthy Caucasian children (52 boys and 40 girls), ranging in age from 6 to 17 years, using the single breath carbon monoxide tech-

FIRST PEEK AT OUR NEW LOW RANGE PEAK FLOW METER

Introducing ASSESS® Low Range for children and patients with limited or severely restricted expiratory flow rates

ASSESS Low Range offers the same standards of excellence as our ASSESS peak flow meter:

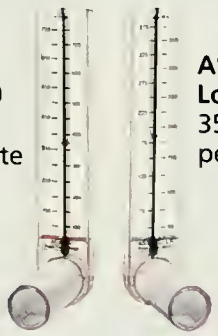
- Reproducible to ±3 liters per minute*
- Proven accuracy† – highly correlated to ATS standards of spirometry*
- Easy to use
- Virtually indestructible
- Unconditional one-year warranty

* Meets *National Asthma Education Program Technical Requirements for Peak Flow Meters*, January, 1991.

†Shapiro S, Hendler J, Ogirala R, Aldrich T, Shapiro MB: An evaluation of the accuracy of Assess and Mini-Wright peak flow meters. *Chest 99*:358-362, 1991.

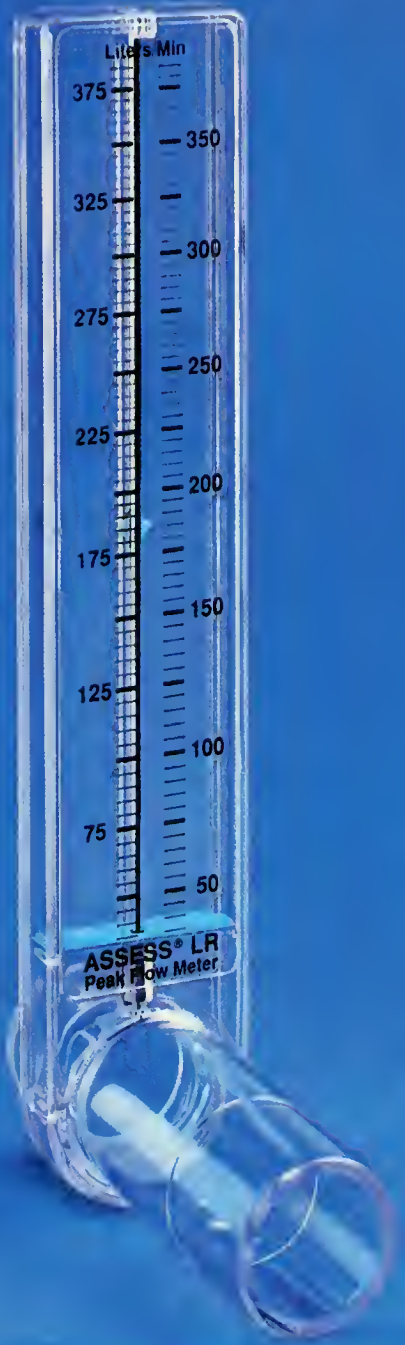
ASSESS® Peak Flow Meter

Setting the standard for peak flow monitoring



ASSESS
60 to 780 liters per minute

ASSESS Low Range
35 to 385 liters per minute



HEALTHSCAN
Products Inc.

☐ Please send product information ☐ Please send an order form

☐ I prefer my patients to order directly. Send patient order forms

NAME (please print)

HOSPITAL

ADDRESS

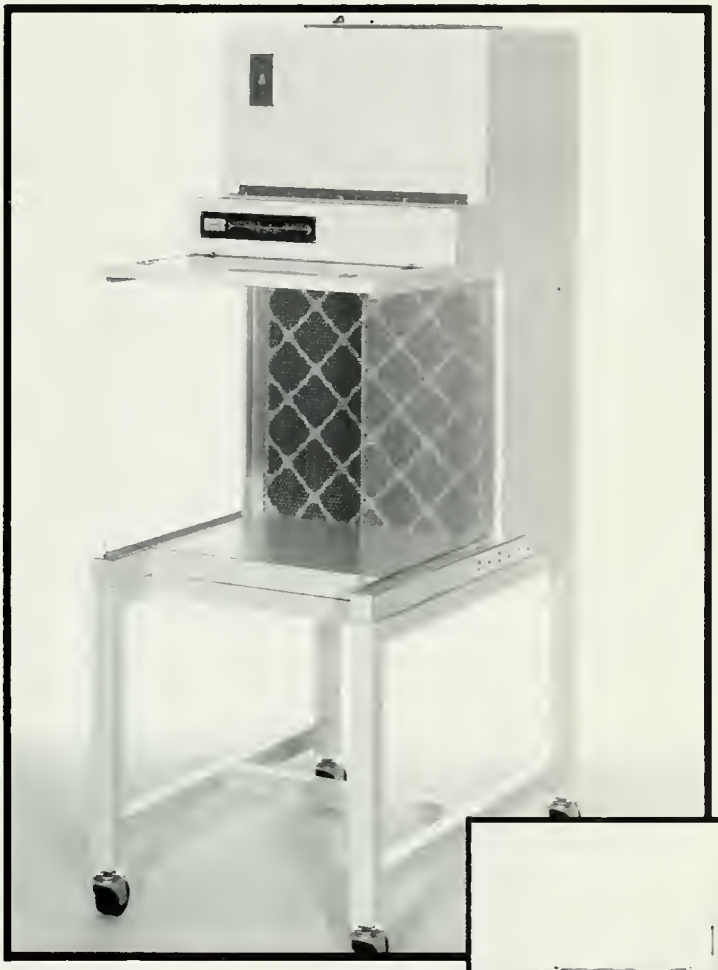
STATE ZIP PHONE

Mail to **HealthScan Products Inc.**, 908 Pompton Avenue, Unit B-2, Cedar Grove, N.J. 07009-1292, or call toll free (800) 962-1266, in New Jersey (201) 857-3414

RC-9/91

Circle 109 on reader service card

AEROSOL TREATMENT GUARD



A
T
G

Protect caregivers from hazardous vapors of aerosolized medication with the HR Aerosol Treatment Guard (ATG). This portable chamber is designed to draw the room air away from the caregiver and around the patient receiving aerosol treatment. 99.99% of all particles larger than *0.3 microns* are captured by the three stage filtration system, before the air returns to the room (particles of aerosolized medication range from 1.0 to 5.0 microns in size). A germicidal UV light is available as an option.

Important benefits include protection for your caregivers, comfort and ease of use, no feeling of isolation by the patient, and reduction in risk of hospital liability.

HR inc
P.O. Box 1744
Bellevue, WA 98009
206/881-7761
206/881-3654 (Fax)

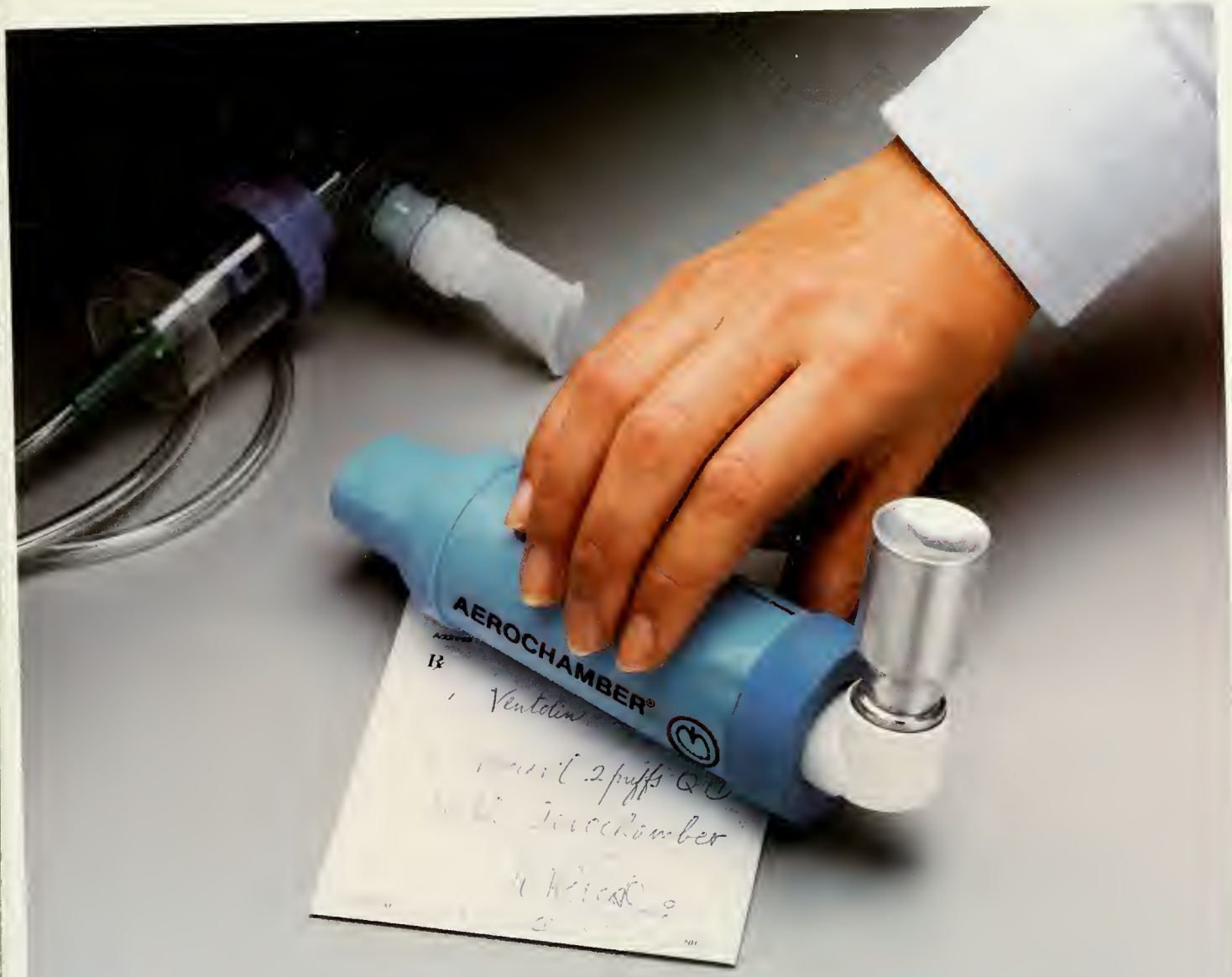
Call For Information
1-800-426-1042

Circle 121 on reader service card

nique (D_{LCO}). Multiple regression equations were developed to predict the D_{LCO} value. Standing height, gender, weight, and age were significant factors in the prediction of D_{LCO}. Sitting height was not a significant covariate when standing height was in the model, but it could replace standing height in the equation. Equations are presented for the calculation of predicted D_{LCO} in children based on standing or sitting height, age, sex, and weight.

Predictors of Neurodevelopmental Outcome Following Bronchopulmonary Dysplasia—JM Luchi, FC Bennett, JC Jackson. AJDC 1991; 145:813.

In infants with bronchopulmonary dysplasia, the influence of the severity of their pulmonary disease on neurodevelopmental outcome is unknown. Neurodevelopmental outcomes at a mean age of 36 months were assessed in 27 premature subjects who had bronchopulmonary dysplasia. Subjects had a mean birth weight of 940 g (range 540 to 1,690 g) and a mean gestational age of 27 weeks (range, 25 to 31 w). The duration of mechanical ventilation ranged from 22 to 128 days, and the duration of requirement of supplemental oxygen ranged from 34 to 1,033 days. No significant correlations were found between duration of mechanical ventilation or oxygen therapy and overall neurodevelopmental outcome. In contrast, cranial ultrasound findings of intracranial hemorrhage and/or periventricular echodensity related specifically to poorer cognitive outcome. By age 3 years, severity of bronchopulmonary dysplasia is not a sufficient predictor of neurodevelopmental outcome. Intracranial hemorrhage and periventricular echodensity continue to be important predictors.



Make The Right Choice

AEROCHAMBER® is fast becoming the choice over Small Volume Nebulizer for better delivery of aerosolized medications. The AEROCHAMBER is as efficient and effective as the use of SVN.[1] With the new FLOWSIGnal™, the patient is encouraged to inhale correctly to obtain the optimum benefit from the medications (MDI). AEROCHAMBER can also provide significant cost savings.[2]

For immediate response to medications with the minimum of time and effort, you now have a choice. When you see all the advantages of AEROCHAMBER compared with SVN, you will agree, AEROCHAMBER is the right choice. *For more information, call or write:*

Improving The Future Today

MONAGHAN MEDICAL CORPORATION

P.O. Box 2805, Plattsburgh, NY 12901 800/833-9653 In NY 518/561-7330 FAX 518/561-5660

(1) Salzman GA, Pyszczynski DP, Journal of Asthma 23(6), 297-310 (1986) A Comparison of Two Delivery Methods for Aerosolized Metaproterenol Sulfate

(2) Ref. Berenberg MJ, Baigelman W, Cupples LA, Pearce L. Comparison of metered dose inhaler attached to an AEROCHAMBER with an updraft nebulizer for the administration of metaproterenol in hospitalized patients. Journal of Asthma, 22: 87–92 (1985)

Circle 139 on reader service card

The following companies were designated as Conference Sponsors and Donors in recognition of their educational grants to the American Respiratory Care Foundation that made the Conference possible. Each Sponsor identified a Respondent to participate in discussions and react to presentations and up to three representatives to act as Observers throughout the conference. Donors identified one or two representatives to act as Observers.

Sponsors:	Observers	Respondents
Allen & Hanburys, Division of Glaxo Inc		
Baxter Healthcare Corp, Pharmaseal Division	Duane Kazal Doug McDowell Tom Michaels	
Boehringer Ingelheim Pharmaceuticals Inc	Joseph Turi PhD S Montgomery PhD	
Hudson Respiratory Care Inc	Anne Watson RRT	Wesley Brown RRT
ICN Pharmaceuticals Inc		Melvin Marks MD
Marquest Medical Products Inc	David Wright	
Monaghan Medical Corp	Michael Amato Mitch Barens Martin Foley	David Geller MD
Pall Biomedical Products	Joseph Parisi	Gerald Smaldone MD
Donors:		
Amaric Pharmaceutical Research Corp	Mary Szalkowski	
DHD Medical Products, Division of Diemolding Corp	Ron McHenry	
Genentech Inc	Kevin Corkery RRT	
Nellcor Inc		
Peace Medical	Frank Fegan Kevin Fegan	

Invited Guests (as observers only): Michael Boroch MBA RRT, Terrance C Coyne MD, Bob Demers RRT, Dale Eiserman, Jim Fink RRT, Lloyd Hayes MD, Sharon McAvinue RN, Sue Marino, Jon Nilsestuen PhD RRT, Alfred Soffer MD, Ted J Witek DrPh RRT

CONSENSUS CONFERENCE ON AEROSOL DELIVERY

A Special Issue

containing the papers and consensus statement
comprising a conference
held January 10-12, 1991, in Cancun, Mexico,
sponsored by the American Association for Respiratory Care
and its science journal RESPIRATORY CARE
and funded through educational grants coordinated by
the American Respiratory Care Foundation

Faculty:

John R Balmes MD—*San Francisco, California*
Richard E Chaisson MD—*Baltimore, Maryland*
Myrna B Dolovich PEng—*Hamilton, Ontario, Canada*
Robert J Fallat MD—*San Francisco, California*
Robert M Kacmarek PhD RRT—*Boston, Massachusetts*
Heinrich Matthys MD—*Freiburg, Germany*
Stephen P Newman PhD—*London, United Kingdom*
R Michael Sly MD—*Washington, District of Columbia*
Nils L Svedmyr MD—*Gothenburg, Sweden*
Donald P Tashkin MD—*Los Angeles, California*
Hetty Waskin MD—*Durham, North Carolina*

Special Adviser:

Scott Deitchman MD PhD—*Cincinnati, Ohio*

Planning-Writing Committee:

Neil R MacIntyre MD, Chairman—*Durham, North Carolina*
Pat Brougher RRT—*Dallas, Texas*
Dean Hess MEd RRT—*York, Pennsylvania*
Michael T Newhouse MD—*Hamilton, Ontario, Canada*
David J Pierson MD—*Seattle, Washington*
Irwin Ziment MD—*Sylmar, California*

Aerosol Therapy: The Hard Questions

Aerosol therapy has been and continues to be one of the most frequently ordered respiratory care treatments in the United States and, indeed, throughout the world. In recent years, we have seen tremendous progress in the development of new drugs to treat the full spectrum of respiratory disease. We are now on the threshold of an era that already has ushered in 'exotic' aerosols for the treatment of the complications of respiratory syncytial virus infections, *Pneumocystis carinii* pneumonia, and respiratory distress syndrome.

There is concern that such drugs may pose a health risk to those who render the therapy and attend the patient. In addition, important questions are being raised regarding the cost benefits of aerosol therapy: (1) Is the procedure 'simple' enough to allow persons who are not formally trained to mix and administer the drugs via the aerosol route? (2) How often and in what doses should specific aerosols be administered? (3) What are the current professional standards for aerosol administration?

These questions and others take on additional importance when one recognizes that the health-care delivery system in this country is teetering on the brink of collapse because of heavy-handed efforts to limit spending. As the the national deficit continues to be the major problem in the United States, its impact on the health-care system must not go unnoticed. It has been estimated that approximately $700 billion will be spent on health care in this country in 1991. This figure represents approximately 13.3% of our gross national product. Many believe that health-care spending levels in this country are too high; whereas others believe that spending levels are adequate but misdirected. Whatever the position, it appears that the policy makers will continue to question medical interventions and by ratcheting down reimbursement will enforce a sort of rationing of health-care resources in this country. We see added to this rationing the latest downsizing strategies undertaken by hospitals, which in some cases involve the handing over of the administration of aerosol treatment to persons who have not been formally trained in respiratory care—a recipe for potential disaster or, at least, a waste of resources in an atmosphere that mandates the husbanding of resources and the administration of efficacious respiratory care!

Large sums of money have been spent on aerosol therapy research, but precious little of the total has been earmarked for applied research. We need to know now, more than ever, what the most effective ways are to administer aerosol therapy. We need to know what resources, human and material, are required to bring about effective aerosol therapy; and, yes, we need to know when aerosol therapy is not effective. As respiratory care practitioners, we must contribute to the solution of problems of health-care delivery and cost rather than continuing to be part of the problem by failing to resolve questions of outcome and efficacy—information that probably should have been developed when the pioneers in respiratory care realized almost 50 years ago that a discrete body of knowledge does exist related to "oxygen therapy."

About 2 years ago, the American Association for Respiratory Care set out to develop national practice standards for various respiratory care modalities and clinical interventions. The first phase of this endeavor was an exhaustive literature search, and one of the consequences of that search was a confirmation of the suspicion that more questions remain unanswered than are answered by the literature. The Association is also concerned about the health and welfare of its practitioners, especially within the context of the administration of exotic aerosols such as pentamidine and ribavirin. It quickly became apparent that a conference to review

the most recent developments in aerosol therapy was in order. We also believed that the necessary gathering of international experts provided an opportunity for an additional product of the conference that heretofore had not been attempted by the Association. That product would be a consensus statement—a benchmark on applied aerosol therapy available to health-care practitioners and policy makers to aid in decision making regarding resources, utilization, clinical effectiveness, and practitioner protection. In this issue of the Journal, you have the opportunity to review that document and the related conference papers. Please bear in mind that the purposes of the conference were to establish consensus on the most efficacious methods of aerosol delivery and to address concerns regarding practitioner protection while administering certain aerosols. Clinical efficacy of the drugs themselves was beyond the scope of this conference.

Many aspects of aerosol therapy are, indeed, controversial, but that is as it should be because no one owns the grand vessel that holds all of the knowledge. I do believe that consistency in practice will prove to be the foundation for future applied clinical research in aerosol therapy, and I do believe that we, as practitioners, should be the first to ask the questions, even the hard questions: Is this therapy necessary? Should we be the ones administering it? If the answer is No—the therapy isn't necessary, and we shouldn't be doing it—then, it is imperative that we be the first to find and accept that negative answer and educate the rest of the health-care provider community. On the other hand, if we are valuable in rendering aerosol therapy and if a specific aerosol therapy is effective in treating the patient, then let's be the first to identify the optimum methods in order to fulfill our commitment to providing the appropriate match between respiratory care resource and respiratory care need. Isn't that a prime directive?

Sam P Giordano MBA RRT
Executive Director
American Association for Respiratory Care
Dallas, Texas

American Association for Respiratory Care

Aerosol Consensus Statement—1991

Introduction

Aerosols are widely used in health care, both in diagnosis and in therapy. In respiratory care, increasing application of aerosols in patient assessment (eg, sputum induction for detection of *Pneumocystis carinii*) and for therapy for both airways dysfunction (eg, bronchodilators in asthma) and parenchymal disease (eg, pentamidine for prophylaxis and treatment of *P carinii* pneumonia) render the subject especially important. Although objective documentation of the superiority of one device or technique over others is often lacking, clinicians must nonetheless make practical choices in administering aerosols to patients. In view of the importance of such choices in the face of an incomplete database, the American Respiratory Care Foundation and the American Association for Respiratory Care and its science journal RESPIRATORY CARE convened a group of authorities recognized for their work in the science and application of aerosols to establish as much consensus as possible to guide the clinician. The participants met for three days in January 1991 to address this task.

Active participants consisted of the faculty (persons with recognized expertise), designated respondents from industry, and the writing committee. Observers from clinical medicine and industry were present but did not participate. The writing committee identified principal topics and issues, each of which was addressed by a member of the faculty in a formal review, followed by discussion with the whole group. After all presentations had been made, the writing committee prepared the initial draft of a working document that was distributed the following morning for consideration by the entire group. In the several hours of ensuing discussion, a surprising degree of consensus was reached on most issues; those for which consensus could not be reached were noted.

Following the conference, the second draft of the consensus statement was submitted to all participants for revision; after editing and further modification, the entire group of participants was once again given the opportunity to comment and approve the final document presented here.

1. Aerosols as Therapy

Certain drugs for the treatment of some lung disorders can have a higher therapeutic index (ie, ratio of desired effects to side effects) when delivered as aerosols than as parenteral or enteral therapy. This has been most clearly shown for a number of drugs designed to treat airway dysfunction (eg, certain beta-adrenergic agonists, anticholinergics, and corticosteroids). It also appears true for certain drugs designed to treat parenchymal disease (pentamidine and ribavirin).

2. Aerosol Physics

Aerosol effectiveness is a function of the dose deposited at the appropriate site in the lungs. *Aerosol deposition* is affected by (a) the amount of aerosol produced and the particle characteristics, (b) ventilatory pattern, and (c) airway anatomy and geometry.

Aerosol amount and particle characteristics are determined by the aerosol generator and the substance aerosolized. In addition, particle characteristics can change (as a function of particle velocity and environmental factors such as temperature and humidity) as particles move from the generator to the lungs. Aerosol particles are often characterized by their mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) of their median aerodynamic diameter. (The MMAD is that diameter around which the mass of particles is equally distributed. The GSD is a measure of the dispersion of particle diameters in the aerosol.) Aerosol particles with a MMAD ≤ 5 μm are ideal for deposition in the lung because oropharyngeal deposition may predominate with MMAD > 5 μm. The depth of penetration of an aerosol into the bronchial tree decreases as aerosol

particle sizes increase. Generally, aerosols with MMADs of 2-5 μm are considered optimal for delivery to the airways, and aerosols with MMADs of 0.8-3.0 μm are considered suitable for drug delivery to the parenchyma. Particles smaller than 0.8 μm are generally exhaled and thus contribute little to the therapeutic effect.

Factors associated with *ventilatory pattern* that affect aerosol deposition include inspiratory flowrate (generally, inspiratory flows of about 0.5 L/s optimize deposition of liquid aerosols, whereas higher flows often appear necessary for the generation and dispersion of dry powder aerosols). Breath-hold at end-inspiration enhances deposition due to particle settling. The magnitude of the tidal volume affects aerosol deposition largely by influencing the amount of aerosol delivered to the lungs.

Anatomic and pathologic factors affecting aerosol delivery involve the diameter of the airways. In general, the narrower the airways (eg, pediatric airways, obstructed adult airways), the less the aerosol deposition distally. Aerosol delivery to the lower respiratory tract is substantially reduced by the presence of an artificial airway (eg, endotracheal tube).

3. Aerosol Generators

Clinical aerosols are generated by (a) nebulizers (jets, ultrasonics), (b) metered dose inhalers (MDI) with and without accessory, or auxiliary devices (eg, actuators, simple spacers, and holding chambers), and (c) dry powder inhalers (DPI).

The output capabilities of *nebulizers* (both amount aerosolized/unit time and particle-size distribution) vary over a wide range depending upon design characteristics. Clinicians must appreciate this variability and be cognizant of the specific characteristics of a given nebulizer in a given clinical setting before using it. Nebulizers should incorporate baffles or settling chambers to reduce large-particle delivery in order to minimize oropharyngeal and large-airway deposition. Mouthpiece delivery is preferable to mask delivery because it avoids nasal deposition and simplifies the creation of a closed system.

Important advantages of nebulizers include ease of administration (ie, once set up, aerosols can be delivered for prolonged periods, with tidal breathing), the capability to aerosolize large volumes (eg, 15-20 mL/h is common for jet nebulizers, with higher volumes/unit time reported for ultrasonics), and the capability to deliver medications not available in MDIs or DPIs. Important disadvantages of nebulizers include low lung deposition related to the use of tidal breathing (generally 2-10% of the dose placed in the nebulizer, although greater deposition can occur under some circumstances), the consequent need for higher doses and longer administration times, the associated costs, and the risk of contamination.

Metered dose inhalers deliver, as a bolus, more concentrated drug aerosols than the solutions commonly available for nebulizers. However, MDIs require proper administration techniques for optimal effect (coordinated actuation, slow inhalation [0.5-0.75 L/s], a deep breath approaching an inspiratory capacity inhalation, and at least a 4-second breath-hold). Consensus could not be reached on whether positioning the MDI mouthpiece 4 centimeters from the open mouth before actuation of the MDI constitutes optimal technique. MDIs can be equipped with devices that automatically couple actuation to inspiratory effort, thus eliminating the need for coordinating hand actuation with inhalation. MDI holding chambers also eliminate the need to coordinate actuation and inhalation. Spacers and holding chambers also decrease particle velocity and reduce the number of large particles. Both of these features reduce oropharyngeal and large-airway deposition with a consequent reduction in systemic absorption.

Deposition of aerosol from an MDI with a spacer or holding chamber is similar to (and perhaps better than) deposition from a properly used MDI alone. Advantages of the MDI are lung deposition of 10-15% of the metered dose with consequent short treatment times, lower costs, and increased convenience. Disadvantages include the need for some patient cooperation, the practical limitations and inconvenience associated with increased dosing regimens, the limited number of currently available drugs, and the present dependence on chlorofluorocarbons for aerosol generation.

Dry powder inhalers (DPIs) are breath actuated but usually require a higher inspiratory flowrate than that required for the MDI or nebulizer. Flowrates

of 1-2 L/s are optimal, but effectiveness can be seen with flowrates as low as 0.5 L/s with some devices. Advantages include the ease of administration and the fact that they do not require chlorofluorocarbon propellants. However, DPIs are limited by the dose that they can provide and by the number of drugs currently available. When a DPI is used properly, deposition appears to be similar to that of a properly used MDI. Disadvantages are (1) they usually are not particle-size-selective, and thus heavy oropharyngeal deposition may occur (similar to an MDI alone), (2) high humidity environments may cause clumping of the powder particles, and (3) DPIs cannot be used in ventilator circuits.

4. Choice of Device

In general, the MDI (or MDI plus spacer or holding chamber) is the most convenient, versatile, and cost-effective way to deliver aerosols. These devices should thus be the first choice for delivery in adults and cooperative children. The DPI may be an acceptable alternative to the MDI when the necessary flowrate can be generated by the patient.

As patients become less able to actuate and coordinate these devices and as their breathing pattern becomes suboptimal, deposition of aerosol in the lung decreases. In addition, as dosing needs increase, repeated MDI use can become inconvenient for both patient and caregiver. Under any of these circumstances, a nebulizer becomes an acceptable alternative delivery device.

In the presence of an endotracheal tube, lung deposition of any aerosol is reduced. For the intubated, mechanically ventilated patient, nebulizers (probably best placed in the manifold) and MDIs (either actuated directly into circuit or into a spacer or holding chamber as close as possible to the endotracheal tube) are both acceptable. Dose adjustments are probably indicated under these circumstances. The best ventilatory pattern and the best aerosol-generation technique for aerosol delivery through endotracheal tubes are not known.

Parenchymal dosing with such drugs as pentamidine and ribavirin requires the use of a nebulizer because of current drug packaging. Particle sizes of 0.8 to 5.0 μm MMAD are optimal for both airway and parenchymal deposition of ribavirin, although the United States Food and Drug Administration has recommended the Small Particle Aerosol Generator (SPAG), which generates ribavirin particles with a MMAD < 1.5 μm, for this purpose in children. Particle sizes less than 3 μm MMAD are appropriate for pentamidine, both to assure parenchymal deposition and to reduce complications from airway deposition, such as cough.

5. Dosing Strategies

Aerosol effectiveness is a function of the dose deposited at the appropriate site in the lung, and this deposition can vary considerably depending upon generator characteristics and other factors. Because of this and because 'standard' manufacturer-recommended dosing guidelines for some airway-specific aerosols (eg, beta agonists and anticholinergics) may not produce a maximal effect in all patients, dosing regimens (ie, doses and frequencies) for these aerosols can be increased under appropriate circumstances (eg, acute airway dysfunction or presence of small-caliber endotracheal tube). Ideally these dose increases should be titrated to carefully monitored *objective* responses. Good data exist supporting the use of higher doses of beta$_2$-selective agonists under these circumstances (eg, MDI doses of up to 20 puffs over a 10-20 minute treatment period, repeated every 20-30 minutes, standard nebulizer doses every 20 minutes, or even continuous nebulization of higher concentrations of the nebulizer solution). However, it must be emphasized that with high-dose beta-agonist regimens, the patient must be properly and continuously monitored for side effects (especially cardiac effects, tremor, and hypokalemia), and the patient must also be treated comprehensively with systemic and other therapies to correct airway dysfunction.

For maintenance therapy for patients with steroid-responsive chronic airway obstruction, high-dose inhaled steroids from an MDI with spacer or holding chamber (to reduce oropharyngeal deposition and resultant complications such as hoarseness and candidiasis) are acceptable (up to 2-mg beclomethasone or equivalent per day). The greater risk of local side effects or some adrenal suppression from these higher doses is preferable to the greater

systemic toxicity of bioequivalent doses of enteral steroids.

At the present time, effectiveness of different doses of ribavirin and pentamidine are not known and, thus, these should only be administered according to manufacturers' recommended dosing schedules. Similarly, newer drugs for parenchymal deposition (eg, other antibiotics, surfactant) should be administered only according to manufacturers' recommendations until more data are available.

6. Special Considerations for Pediatric Aerosol Delivery

Much less information exists on aerosol delivery in the pediatric age groups (especially neonates and infants) than in the adult. Specific neonatal and pediatric considerations include smaller airway size, lack of patient coordination, high respiratory rate, short inspiratory time, and decreased ability to breath-hold. Aerosol generators currently used for adults can deliver drugs that produce a physiologic response in infants and children despite deposition that is often less than that occuring in adults (in particular, as low as 1% of the dose placed in the nebulizer, with nose breathing or intubation).

MDIs can be used effectively in children. However, because of the inability of many pediatric patients younger than 10 years of age to coordinate the actuation of the MDI, a holding chamber should always be used. A holding chamber with mask should be used in those less than 3 years of age. A simple spacer or a holding chamber should be used with inhaled steroids for pediatric patients of any age. DPIs may be used in children capable of producing an adequate inspiratory flow. Proper techniques for use of MDIs and DPIs must be periodically reinforced. Because the delivery of aerosols to the lower respiratory tract is less efficient in children than in adults, the number of puffs from an MDI should not necessarily be reduced because of the patient's size. Dosages greater than the manufacturer-recommended dose for children may be required (eg, bronchodilators, cromolyn sodium, and inhaled steroids), and should be tailored to each patient's individual response.

Aerosolized medications can be administered to intubated infants and children. In-line MDIs should not be used in mechanically ventilated infants with a tidal volume less than 100 mL because of the potential hypoxic mixture that results from the volume of chlorofluorocarbon gas released from the MDI. In ventilated children with a tidal volume exceeding 100 mL, an in-line MDI can be used provided the tidal volume exceeds the volume of the MDI adapter, spacer, or holding chamber. MDIs should be administered one puff at a time. When nebulizers driven by an external gas source are used with mechanically ventilated infants and children, care must be taken to avoid excessive increases in tidal volume and airway pressure (particularly with volume ventilators).

Ribavirin can be administered to mechanically ventilated pediatric patients. When this is done, care must be taken (1) to choose a generator with appropriate characteristics, (2) to isolate the ventilator and exhalation valve from the aerosol in order to protect the ventilator and alarm functions (which may require frequent filter and circuit changes), and (3) to protect caregivers and the environment (see below).

7. Aspects of the Clinical Use of Pentamidine and Ribavirin Aerosols of Concern to Those Caring for the Patient

Aerosolized pentamidine and ribavirin are released into the environment because of the design of the systems by which they are administered, through leakage from hoods and canopies, through disconnection of the device from the patient (eg, during coughing or from lack of cooperation), and through patient exhalation and incomplete exhaust filtration.

Some biologic evidence (eg, detection of drug in blood or body fluids) exists for caregiver exposure to aerosolized ribavirin and pentamidine. Given that pentamidine and ribavirin can be topically irritating, can be absorbed systemically after aerosol inhalation, can be retained in the body, and can potentially produce cumulative organ damage, such environmental exposure constitutes a potential health risk to the caregiver. At present, insufficient data are available to permit

either quantitation of the magnitude of this risk or dismissal of its clinical importance.

In addition to these potential hazards of direct exposure to the drug, patients infected with the human immunodeficiency virus (HIV positive) have an increased prevalence of pulmonary tuberculosis. Cough induced by aerosols (eg, pentamidine or hypertonic saline as used for sputum induction) in HIV-positive patients and others places caregivers at increased risk of infection with *Mycobacterium tuberculosis*.

For caregiver protection during the delivery of ***pentamidine***, the following are important:

(1) Prompt recognition and treatment (prophylactic or therapeutic) of tuberculosis in HIV-positive patients is of primary importance in reducing the transmission of infection to caregivers and others.

(2) To reduce potential risk to caregivers, both administration of aerosolized pentamidine and sputum induction should be carried out in facilities that fulfill the CDC guidelines for prevention of transmission of tuberculosis.[1] These include

(a) six air exchanges per hour to the outside or through a HEPA filter and

(b) a negative pressure room (ie, air flows into the treatment room from surrounding rooms and hallways).

(3) Recommended characteristics of nebulizer systems for pentamidine aerosol are

(a) Particle size less than 3.0 μm MMAD under manufacturers' recommended flow conditions, both to reduce cough and to maximize alveolar deposition, and

(b) Construction and use such that output of drug to the environment is minimized (eg, mouthpiece, noseclips, exhalation filters, nebulization only during inspiration, reservoir bag).

For caregiver protection during the delivery of ***ribavirin*** the following are important:

(1) Use of single-patient room, in compliance with ASHRAE guidelines:[2]

(a) six air exchanges per hour to the outside or through a HEPA filter and

(b) a negative pressure room (ie, air flows into the treatment room from surrounding rooms and hallways).

(2) Use of procedures designed to reduce release of drug into the environment. These include

(a) Use of aerosol-containment canopies for spontaneously breathing patients and exhalation filters for ventilated patients. In addition, engineering controls (such as scavenging systems) should be used when the drug is being administered to spontaneously breathing patients.

(b) Interruption of administration prior to and during direct patient care.

(3) Use of full barrier protection (eg, goggles, personal respirator mask, gown, gloves) for special circumstances in which caregivers and others have substantial contact with the drug (eg, during aerosol preparation or direct patient care during aerosolization).

(4) A policy to exclude pregnant and lactating women and persons with previous reactions to ribavirin from contact with the drug.

Insufficient data are currently available for definitive statements regarding caregiver exposure to aerosolized surfactant, antimicrobials other than pentamidine and ribavirin, and other substances currently being administered to patients by aerosol.

8. Aspects of the Clinical Use of Aerosols of Worldwide Environmental Concern

Although small (0.4-0.5% of worldwide production), the medical use of chlorofluorocarbons (CFCs) in pressurized aerosols is of environmental concern. A worldwide ban on CFC use has been recommended to commence by the year 2000. The pharmaceutical industry is encouraged to continue to develop substitute techniques (eg, dry powder) or propellants that are clinically acceptable and environmentally safe. Because such development and subsequent safety testing will be complex and will take 5-10 years under present mechanisms, consideration should be given by governmental

1. U.S. Department of Health & Human Services. Guidelines for preventing the transmission of tuberculosis in health-care settings with special focus on HIV-related issues. MMWR 1990;39(RR-17):20-22.

2. 1987 ASHRAE Handbook. American Society of Heating, Refrigerating, and Air Conditioning Engineers (ASHRAE). Atlanta GA, 1987.

regulatory agencies to the formulation of a special schedule for expediting FDA approval or to extending the time period for the medical use of CFCs in MDIs.

9. Focus of Future Research

Further research is needed. Important topics to be addressed are

(1) Development of more efficient systems to improve aerosol delivery in a cost-effective manner. This is particularly important for aerosol delivery through endotracheal tubes. The relative merits of jet (pneumatic) versus ultrasonic nebulizers versus other systems need to be evaluated.

(2) Development of more appropriate dosing regimens for all types of aerosols. Consideration needs to be given to the device, the nature of the airway, the breathing pattern, the target site in the lung, and appropriate monitoring.

(3) The use of submicronic aerosols in small infants and intubated pediatric patients.

(4) Development of alternatives to chlorofluorocarbon propellants (eg, multidose powder inhalers; devices independent of patient coordination and ventilatory pattern).

(5) Continued surveillance and long-term follow-up of caregivers exposed to ribavirin and pentamidine to identify potential long-term or delayed adverse effects.

(6) In the future in light of (4) and (5), consideration should be given to environmental and occupational exposures as a drug is being developed—not after marketing has already begun.

Faculty:
John R Balmes MD, San Francisco CA
Richard Chaisson MD, Baltimore MD
Myrna B Dolovich PEng, Hamilton, Ontario, Canada
Robert Fallat MD, San Francisco CA
Robert M Kacmarek PhD RRT, Boston MA
Heinrich Matthys MD, Freiburg, Germany
Stephen Newman PhD, London, United Kingdom
R Michael Sly MD, Washington DC
Nils L Svedmyr MD, Gothenburg, Sweden
Donald P Tashkin MD, Los Angeles CA
Hetty Waskin MD, Durham NC

Special Adviser:
Scott Deitchman MD PhD, Cincinnati OH

Planning-Writing Committee:
Neil R MacIntyre MD, Durham NC, Chairman
Pat Brougher RRT, Dallas TX
Dean Hess MEd RRT, York PA
Michael T Newhouse MD, Hamilton, Ontario, Canada
David J Pierson MD, Seattle WA
Irwin Ziment MD, Sylmar CA

Clinical Advantages of the Aerosol Route of Drug Administration

Nils Svedmyr MD

Introduction

Historians tell us that Hippocrates recommended steam inhalations for airway disease more than 2,000 years ago (perhaps one of the earliest prescriptions for inhalation therapy), and the inhalation of anticholinergics was recommended for asthma attacks 200 years ago in the form of cigarettes containing the leaves of *Datura stramonium*. Most inhalation therapy today is for asthma, which is the focus of this paper.

The lung, with a total surface area of some 80 m^2, is the major point of contact between our body and the environment. An elaborate system of host defense mechanisms has evolved to cope with noxious inhaled substances. A lot of work has been performed to develop appropriate inhalation devices, and a lot of time has been spent in trying to teach asthmatics to use these devices correctly. However, even with good devices and good technique, asthmatics retain only a few milligrams (or even micrograms) of inhaled drug in their lungs; but because a few key processes in asthma pathogenesis are surface processes and because we now have potent drugs, inhalation therapy provides optimal therapeutic efficacy with a minimum of side effects. The main advantage of inhalation therapy in asthma is the presence of fewer side effects than are seen after systemic administration. In addition, in some situations, side effects may prevent a drug from exerting its maximal action when it is administered systemically, and in such situations the therapeutic efficacy is better after inhalation.

For some drugs (eg, sodium cromoglycate) inhalation is a prerequisite for effect because the drug is ineffective by the systemic route. In the case of sympathomimetics and anticholinergics, inhalation produces, above all, fewer side effects than are produced by systemic administration. Similarly, inhaled potent steroids have been shown to be the most effective prophylactic maintenance therapy of asthma without causing the serious complications usually seen during long-term treatment with systemic steroids.

Bronchodilating Drugs

Both beta-adrenoceptor stimulants and theophylline have several effects besides bronchodilation that may be of clinical importance in severe acute asthma. Effects of both beta stimulants and theophylline suggested to be of clinical importance are[1]

- relaxation of bronchial smooth muscle (functional antagonism);
- increase in mucociliary transport;
- inhibition of mediator release;
- suppression of permeability edema;
- improved contractility of fatigued diaphragmatic muscle; and
- decrease of pulmonary hypertension, and increase in right ventricular ejection fraction.

In man, all these effects of sympathomimetics are mediated solely by beta$_2$ receptors. The bron-

Dr Svedmyr is associated with the Dept of Clinical Pharmacology, Sahlgrenska University Hospital, Gothenburg, Sweden.

A version of this paper was presented by Dr Svedmyr during the Consensus Conference on Aerosol Delivery, sponsored by the American Association for Respiratory Care, the American Respiratory Care Foundation, and the journal RESPIRATORY CARE, January 10-12, 1991, in Cancun, Mexico.

Reprints: Nils Svedmyr MD, Dept of Clinical Pharmacology, Sahlgrenska University Hospital, S-413 45 Gothenburg, Sweden.

chial smooth-muscle relaxation is probably most important. However, inhibition of permeability oedema and effects on mucus removal from the airways may also be of importance in acute situations.

Circulatory side effects of adrenoceptor stimulation could be due to stimulation of beta receptors in either peripheral vessels or in the heart. An important reason for tachycardia during $beta_2$-agonist treatment is the vasodilation and reflex tachycardia mediated by $beta_2$ adrenoceptors in peripheral vessels.[2-5] In the heart, most beta receptors are of the $beta_1$ subtype. However, in the human heart both $beta_1$ and $beta_2$ adrenoceptors have been shown to mediate an increased heart rate. $Beta_2$ adrenoceptors have been shown to be responsible for 20% of the chronotropic effect, whereas $beta_1$ adrenoceptors almost solely mediate inotropic effects.[6,7] Thus, it is possible that $beta_2$-adrenoceptor agonists induce tachycardia both by a reflex from peripheral vasodilation and by a direct effect on $beta_2$ adrenoceptors in the heart. If $beta_2$ agonists are to be administered, direct stimulation of the $beta_2$ receptors in the heart can only be avoided by administration of the $beta_2$ agonist by inhalation.

In-Vitro Effects on Human Bronchial Muscle

Beta-adrenoceptor agonists and various xanthine derivatives have the same maximal relaxant effect on isolated human bronchial muscle in vitro contracted by a moderate concentration of carbachol (Fig. 1).[8] The relative potency of the drugs in vitro is proportional to their clinical potency. The dose required to relax the muscle is increased as the intensity of the contraction increases.[9-12] Much higher doses are also necessary to relax the muscles in severe acute asthma. Unless there is development of substantial tolerance in situ in asthmatic patients to some of these drugs, there is no reason to believe that the clinical efficacy differs substantially between these two drug classes. In fact, no clinical studies show differences in maximal antiasthmatic effects when these drugs are given in optimal doses by the same route of administration. However, the side effects of these drugs differ, and side effects can make it impossible to achieve the maximal bronchodilating effect in patients with a single drug, especially if the drug is given systemically. Unfortunately, theophylline cannot be given by inhalation because of its irritant effect, which induces bronchoconstriction. This favours inhaled $beta_2$ agonists in acute asthma attacks.

Routes of Administration

Intravenous Sympathomimetics

Figure 2 shows one of our early studies[3] in which isoproterenol (isoprenaline) and albuterol (salbutamol) were infused intravenously in increasing doses so that complete dose-response curves were obtained in a crossover study in asthmatics. Both drugs attained the same maximal bronchodilating effect just as in vitro. The bronchodilator and cardiac stimulant effects of isoproterenol run parallel, suggesting that $beta_1$ and $beta_2$ receptors are equally stimulated. However, with a very high dose of isoproterenol and the achievement of maximal bronchodilation, the heart rate continues to increase until it is nearly double at

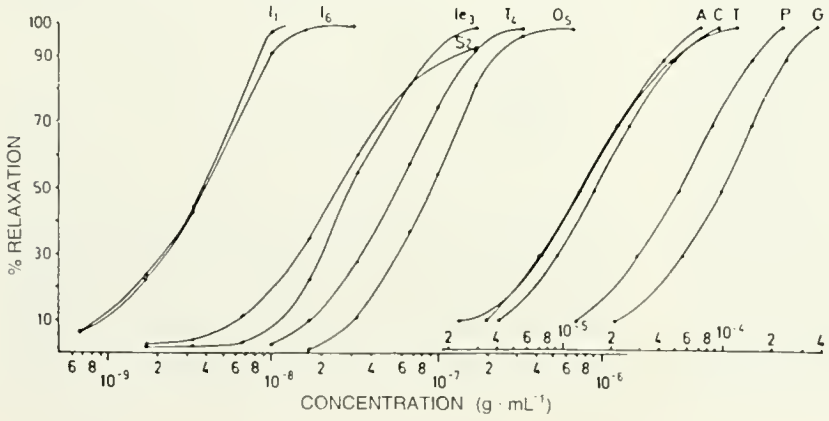


Fig. 1. Dose-response curves for different beta adrenostimulants and theophylline preparations on carbacholine-contracted human bronchial muscle in vitro. Means from 13 experiments. I_1 isoproterenol given as first drug; I_6 isoprenaline as the sixth drug; S_2 = salbutamol, I_3 = isoetharine, T_4 = terbutaline, O_5 = orciprenaline. A = aminophylline. C = choline theophyllinate. T = theophylline sodium-glycinate. P = proxyphylline. G = glyphylline or diphylline.

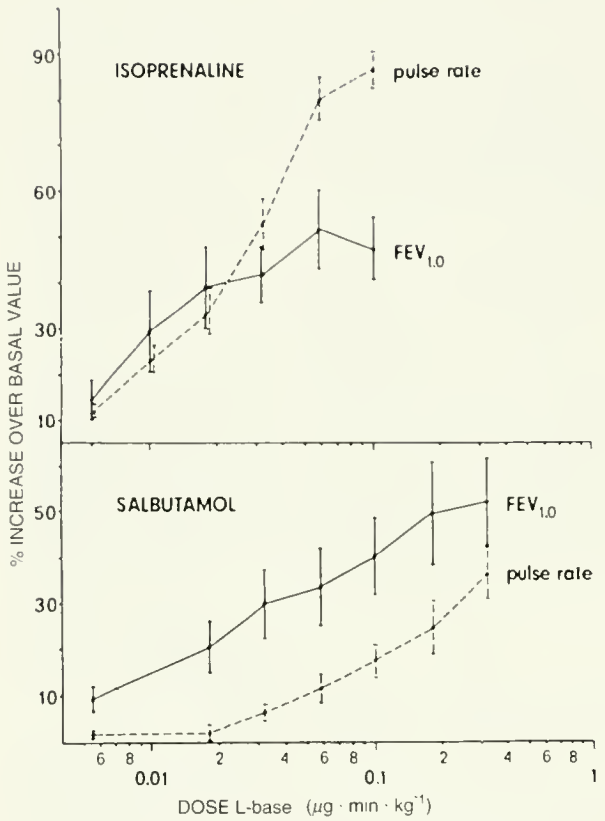


Fig. 2. Mean dose-response curves ± SEM for isoprenaline and salbutamol for 10 patients with asthma. Each dose was infused during 6 min at 30-min intervals. (Modified, with permission, from Reference 3.)

the highest dose. This limits the use of intravenous isoproterenol in severe acute asthma when a high dose is needed to give maximal bronchodilation. (However, I have observed that isoproterenol is still used in some pediatric clinics in very severe acute asthma attacks.) In the same patients, the selective beta$_2$ stimulant (albuterol) gave the same maximum bronchodilation, but was initially not associated with any pulse increase. The pulse did not begin to increase until almost half of the maximum bronchial relaxation had been achieved, but thereafter the pulse did increase with increasing albuterol doses. Thus, even with selective beta$_2$ stimulants, it is not possible to achieve maximum bronchodilation in severely obstructed patients without a simultaneous, relatively pronounced increase in pulse rate if the drug is administered intravenously. Similar results were attained by Paterson et al.[13] By contrast, the increase in heart rate and FEV_1 with metaproterenol began at the same dose (as with isoproterenol).[14]

Inhaled Beta$_2$ Agonists

In another study, we compared, under controlled conditions with complete dose-response curves in a crossover study, the effects of terbutaline given by inhalation and the intravenous route.[4]

Intravenous terbutaline in the upper range of recommended doses did not produce maximal relaxation of the bronchial muscle in patients with endogenous asthma (Fig. 3), but it did increase the heart rate by 25 beats/min and more than doubled the skeletal muscle tremor.[4] When terbutaline was given by inhalation, the same degree of bronchial

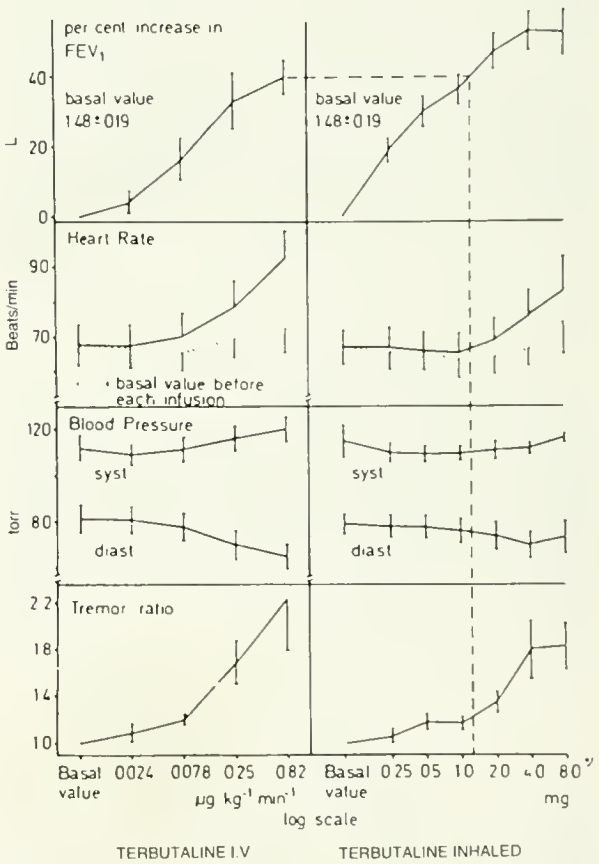


Fig. 3. Effects of increasing doses of terbutaline by intravenous infusion (during 6 min) and dose aerosol on FEV_1, heart rate, blood pressure, and skeletal muscle tremor in asthmatics. (Dotted line = heart rate immediately before the next dose.) Means ± SEM from 10 patients. (Modified, with permission, from Reference 4.)

relaxation was obtained without any effect on heart rate, blood pressure, or tremor, indicating a local effect and increased therapeutic breadth. With higher inhaled terbutaline doses, the maximum bronchodilation was more pronounced than after the highest intravenous dose. The acute margin of safety was notable, with the increase of pulse rate being only 16 beats/min after 63 inhalations of this relatively long-acting substance given cumulatively during 150 min. These side effects are barely noticeable subjectively, so that high inhaled doses may be considered in severe acute asthma not responding to the usual doses. Such high doses can also be administered by continuous nebulization or by a metered dose inhaler (MDI) with a large spacer.

In a recent study, intravenous albuterol (5 μg/kg) was compared to inhaled albuterol (0.15 mg/kg, 1:30 in relation) in a crossover study in 12 asthma patients in a stable phase. As is shown in Figure 4, the peak plasma concentration was more than doubled with the intravenous route, and heart rate increased considerably more with a more pronounced decrease of serum potassium. The bronchodilating effect was, however, more pronounced after inhalation.[15]

Fenoterol, albuterol, and terbutaline are usually regarded as equally $beta_2$ selective, and they are more selective than metaproterenol. However, fenoterol is a full agonist on the $beta_1$ adrenoceptor, whereas albuterol and terbutaline are weak partial agonists on that receptor.[16-19] Therefore, I believe that albuterol and terbutaline are to be preferred in emergency treatment of asthma when very high doses are utilized.

These and other similar studies in moderate severe asthma favour aerosol inhalation as the administration route of choice. In theory, aerosol administration has the definite advantages of providing for direct delivery of the drug into the lung, resulting in an increased selectivity of action. Consequently, inhalation is the superior route of administration for $beta_2$ stimulants if the patient is able to use the inhaler in a proper way. Better bronchodilation may be obtained with cumulative inhalations than with a single high dose if the inhalations are administered with at least 10- to 15-minute intervals between.[20,21]

Does Tolerance to Beta-Receptor Agonists Develop?

During the 1970s, concern (especially in the United States) about the development of tolerance to $beta_2$-adrenoceptor stimulants favoured the use of intravenous theophylline for emergency treatment of asthma. Inhalation of beta agonists was

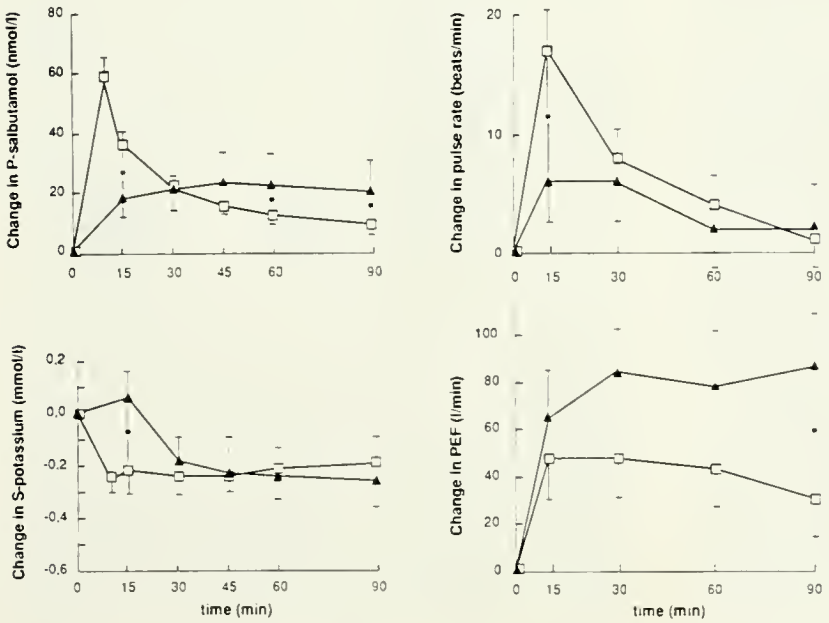


Fig. 4. Plasma concentrations, systemic effects, and ventilatory effects after salbutamol treatment by inhaled route (0.15 mg/kg inhaled during 10-15 min from a nebulizer) (open squares) or by intravenous route (5 μg/kg during 10 min) (closed triangles). (Modified, with permission, from Reference 15.)

also regarded as less effective because severe airway obstruction was believed to attenuate the access of inhaled drugs to lower airways. Today there is general agreement that tolerance to beta sympathomimetics is not a clinical problem even in emergency treatment of acute asthma.[22-25]

Are Intravenous and Inhaled Beta$_2$ Agonists as Effective in Acute Severe Asthma as in Moderately Severe Asthma?

Intravenous Beta Agonists in Severe Acute Asthma

Mechanical ventilation was introduced as the first effective treatment for acute life-threatening asthma. In the early 1970s, Wood et al[26] and Downs et al[27] showed that mechanical ventilation could be avoided in many children by intravenous infusion of high doses of isoproterenol. Parry et al[28] and Herman et al[29] also reported similar results with intravenous isoproterenol. Due to its nonselectivity, however, isoproterenol infusion has been reported to be associated with myocardial ischaemia and also sudden deaths caused by myocardial infarction.[30-32] Furthermore, intravenous isoproterenol has never been studied in a controlled manner as treatment of severe acute asthma, in spite of significant therapeutic risks. However, I have observed that it is still used in some pediatric clinics.

In the mid-1970s, it was shown in several studies that intravenous albuterol and terbutaline produced good bronchodilation with few side effects even in acute severe asthma.[33-35] Intravenous beta$_2$ agonists were shown to be as effective as intravenous theophylline.[36-39] If an intravenous beta agonist is used, a selective beta$_2$ agonist (albuterol and terbutaline) is preferred.

In acute severe asthma, patients often present with tachycardia due to the asthma attack. Therefore, treatment with a beta-stimulating drug that decreases airway resistance also leads to a decrease in the respiratory effort needed by the patient. That is why in some studies of acute severe asthma, a fall in heart rate occurs even after treatment with intravenous beta-stimulating drugs[25] and after high doses of inhaled beta$_2$ agonists.[40-44]

Inhaled Beta Agonists in Severe Acute Asthma

Despite the argument that parenteral administration should theoretically be more effective than inhalation therapy in severe acute asthma, studies have failed to show that intravenous beta$_2$ agonists are more effective than inhalation.[40,45-49] In all these studies, inhalation was at least as effective as intravenous administration but produced fewer side effects.

Lawford et al[40] compared albuterol by inhalation and by the intravenous route with a parallel group design in 16 patients with severe acute asthma. Two patients were withdrawn from intravenous albuterol because of side effects. The intravenous dose of albuterol was high—900 μg—and the ventilatory effect was equal for the intravenous and inhaled route, whereas heart rate increased by 19 beats/min after I.V. treatment but decreased by 10 beats/min after inhalation.

In 1980, the first well-controlled clinical trials showed that repeated aerosol administration of beta$_2$ agonists with short intervals was more effective than parenteral administration of both beta agonists and theophylline in severe acute asthma, as shown by McFadden and his group.[50-52] They showed that isoproterenol 2.5 mg inhaled 3 times every 20 min gave as good an antiasthmatic effect when combined with the placebo infusion as when it was administered together with an acute loading dose of aminophylline. This was the first controlled study challenging the use of intravenous theophylline in acute severe asthma. Furthermore, with modern selective long-acting beta$_2$-adrenoceptor stimulants, such as albuterol and terbutaline, it is possible to achieve even better bronchodilation with fewer cardiovascular side effects than with isoproterenol. Addition of aminophylline only increases the toxicity, not the efficacy of inhaled metaproterenol in acute exacerbations of asthma.[53] These and many other studies have shown that the importance of theophylline in the emergency treatment of asthma was overemphasized and today intravenous theophylline is regarded as the third-line drug in acute severe asthma, after inhaled beta$_2$ agonists and inhaled anticholinergics.[54]

McFadden's group also showed that asthmatics may be successfully treated with inhaled beta agonists irrespective of their medication history, a strong indication that tachyphylaxis is not clinically relevant.[22]

A Swedish multicentre study[25] of 176 patients compared treatment with 2 doses of nebulized albuterol (0.15 mg/kg), given at 30-min intervals, with intravenous albuterol (0.5 μg/kg) (Fig. 5). A significantly larger increase in peak expiratory flow (PEF) was seen after the first inhaled dose compared to intravenous treatment, but no differences in side effects were seen between the groups. After a second inhaled dose, a further increase was seen in PEF but also in systemic side effects. This is further strong evidence of the superiority of the inhalation route of albuterol administration in the treatment of severe acute asthma and permits recommendation of inhaled nebulized albuterol as first-line treatment of acute asthma. The trial also failed to show a beneficial effect of intravenous administration of theophylline in patients treated with inhaled albuterol, whereas theophylline induced a further effect after intravenous albuterol.

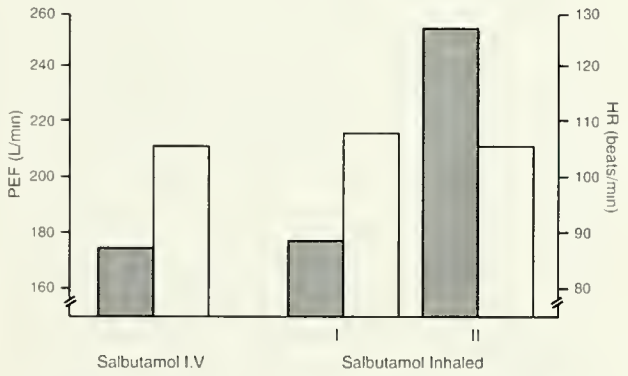


Fig. 5. Mean peak expiratory flow (PEF) values ■ and heart rate □ in a parallel group study of 176 patients with acute severe asthma treated either with intravenous salbutamol (5 μg/kg) or with inhaled salbutamol (0.15 mg/kg), inhaled in two periods 30 min apart (I & II). Basal PEF values were (166 ± 70 and 170 ± 47 L/min) and heart rate (111 ± 10 and 112 ± 9 beats/min) in the intravenous and inhalation groups, respectively. (Adapted, with permission, from Reference 25.)

Duration of Action

The duration of action of inhaled bronchodilators is shorter in severe acute asthma for several reasons:

(1) Low tidal volume and pathologically narrowed airways reduce the delivered dose to lower airways and the peripheral distribution.[55,56]

(2) Maximal bronchodilation at the top of the time-effect curve is desired.

(3) In highly increased smooth-muscle tone, an increased concentration of bronchodilators is necessary to induce maximal bronchodilation.

(4) A slight tachyphylaxis due to heavy use of inhaled beta agonists before admission may be seen in some patients—mainly as a shorter duration of bronchodilation with preserved maximal effect.[57,58]

For this reason, a higher dose and more frequent administration may be required in severe acute asthma. Several textbooks suggest a dosage interval of 4 hours, although in many hospitals I have observed 1-2 hours to be more common. However, even with this short dose interval, it is commonly noted that some patients with severe acute asthma improve initially, but then become worse before the next dose is given. Several recent studies in children have shown that very high doses can be given by the inhalation route at 30-min intervals or by continuous nebulization.[41-44]

In those patients not achieving adequate bronchodilation with high doses of beta$_2$ agonists frequently administered, anticholinergics (ipratropium bromide) are considered a second-line drug before intravenous theophylline because of the sometimes life-threatening side effects of the theophylline.[59,60] Ipratropium bromide should be given in a dose of 0.25 mg in children or 0.5 mg in adults if a jet nebulizer is used. With these doses no systemic side effects are seen at all.

Corticosteroids, given by inhalation, are today first-line drugs for the maintenance treatment of asthmatics, as mentioned in my introduction. Steroids (at least those without mineralocorticoid side effects) have practically no acute side effects, however. They are therefore given systemically in severe acute asthma.[61]

Summary

Several controlled studies during recent years have clearly shown that inhaled $beta_2$ agonists in high doses, given frequently or by continuous nebulization, are the first-line treatment of severe acute asthma. In patients not achieving adequate bronchodilation with this therapy, inhaled anticholinergics should also be given. Intravenous theophylline is today usually regarded as the third-line drug, and is reserved for patients not responding to this combined treatment. Corticosteroids should always be given in severe acute asthma, but because of their lack of acute side effects should be given by the intravenous or oral route.

REFERENCES

1. Svedmyr N, Lofdahl C-G. Physiology and pharmacodynamics of beta-adrenergic agonists. In: Jenne JW, Murphy S, eds. Drug therapy for asthma: research and clinical practice. New York: Marcel Dekker Inc, 1987: 177-211.
2. Robillson BF, Epstein SE, Beiser GD, Braunwald E. Control of heart rate by the autonomic nervous system. Circulation Res 1966;19:400-411.
3. Svedmyr N, Thiringer G. The effects of salbutamol and isoprenaline on beta-receptors in patients with chronic obstructive lung disease. Postgrad Med J 1971;47:44-46.
4. Thiringer G, Svedmyr N. Comparison of infused and inhaled terbutaline in patients with asthma. Scand J Respir Dis 1976;57:17-24.
5. Arnold JM, McDevitt DG. Heart rate and blood pressure responses to intravenous boluses of isoprenaline in the presence of propranolol, practolol and atropine. Br J Clin Pharmacol 1983;16:175-184.
6. Brown JE, McLeod AA, Shand W. Evidence for cardiac adrenoceptors in man. Clin Pharmacol Ther 1983;33: 424
7. Stiles GL, Taylor S, Lefkowitz RJ. Human cardiac beta-adrenergic receptors: sub-type heterogeneity delineated by direct radioligand binding. Life Sci 1983;33:467-473.
8. Svedmyr N. Treatment with beta-adrenostimulants. Scand J Respir Dis 1977;101(Suppl):59-69.
9. Karlsson J-A, Persson CG. Influence of tracheal contraction on relaxant effects in vitro of theophylline and isoprenaline. Br J Pharmacol 1981;74:73-79.
10. Raffestin B, Cerrina J, Boullet C, Labat C, Benveniste J, Brink C. Response and sensitivity of isolated human pulmonary muscle preparations to pharmacological agents. J Pharmacol Exper Ther 1985;233:186-194.
11. Jenne JW, Shaughnessy TK, Druz WS, Manfredy CJ, Westal RE. In vivo functional antagonism between isoproterenol and bronchoconstrictance in the dog. J Appl Physiol 1987;63:812-819.
12. Van Amsterdam RGM, Meurs H, Ten-Berge REJ, Veninga NC, Brouwer F, Zaagsma J. Role of phosphoinositide metabolism in human bronchial smooth muscle contraction and in functional antagonism by beta-adrenoceptor agonists. Am Rev Respir Dis 1990; 142:1124-1128.
13. Paterson JW, Evans RJC, Prime FJ. Selectivity of bronchodilator action of salbutamol in asthmatic patients. Br J Dis Chest 1971;65:21-38.
14. McEvoy JDS, Vall-Spynosa A, Paterson JW. Assessment of orciprenaline and isoproterenol infusions in asthmatic patients. Am Rev Respir Dis 1973;108:490-500.
15. Janson C. Inhaled and intravenous salbutamol: a study of plasma levels and effects. Eur J Respir Dis (in press) 1991.
16. Tandom MK. Cardiopulmonary effects of fenoterol and salbutamol aerosols. Chest 1980;77:429-431.
17. Brittain RT, Dean CM, Jack D. Sympathomimetic bronchodilator drugs. Pharmacol Ther Bull 1976;2:423-462.
18. Flatt A, Crane J, Purdie G, Kwong T, Beasley R, Burgess C. The cardiovascular effects of beta adrenergic agonist drugs administered by nebulisation. Postgrad Med J 1990;66:98-101.
19. Windom HH, Burgess CD, Siebers RWL, Purdie G, Pearce N, Crane J, et al. The pulmonary and extrapulmonary effects of inhaled beta-agonists in patients with asthma. Clin Pharmacol Ther 1990;48:296-301.
20. Dulfano MJ, Glass P, McPhillips JJ. A comparison of the bronchodilator effects of the same amounts of terbutaline aerosol given as a single or in divided doses. Ann Allergy 1977;39:266-271.
21. Heimer D, Shim C, Williams MH. The effect of sequential inhalations of metaproterenol aerosol in asthma. J Allergy Clin Immunol 1980;66:75-77.
22. Rossing TH, Fanta CH, McFadden ER Jr. Effect of outpatient treatment of asthma with beta-agonists on the response to sympathomimetics in an emergency room. Am J Med 1983;75:781-784.
23. Svedmyr N. Is beta-adrenoceptor sensitivity a limiting factor in asthma therapy? In: Morley J, ed. Beta-adrenoceptors in asthma. London: Academic Press, 1984:181-199.
24. Tattersfield AE. Tolerance to beta-agonists. Bull Eur Physiopathol Respir (Clin Respir Physiol) 1985;21 (Suppl):1S-5S.
25. Swedish Society of Chest Medicine. High-dose inhaled versus intravenous salbutamol combined with theophylline in severe acute asthma. Eur Respir J 1990;3:163-170.
26. Wood DW, Downs JJ, Scheinkopf H, Leeks III. Intravenous isoproterenol in the management of respiratory failure in childhood status asthmaticus. J Allergy Clin Immunol 1972;50(2):75-81.

27. Downs JJ, Wood DW, Harwood I, Scheinkopf HN, Raphaly RC. Intravenous isoproterenol infusion in children with severe hypercapnia due to status asthmaticus. Crit Care Med 1973;1(2):63-68.
28. Parry WH, Martorano F, Cotton EK. Management of life-threatening asthma with intravenous isoproterenol infusions. Am J Dis Child 1976;130:39-42.
29. Herman JJ, Noah ZL, Moody RR. Use of intravenous isoproterenol for status asthmaticus in children. Crit Care Med 1983;11(9):716-720.
30. Matson JR, Loughlin GM, Strunk RC. Myocardial ischemia complicating the use of isoproterenol in asthmatic children. J Pediatr 1978;92:776-778.
31. Kurland G, Williams J, Lewiston NJ. Fatal myocardial toxicity during continuous infusion intravenous isoproterenol therapy of asthma. J Allergy Clin Immunol 1979;63:407-411.
32. Maguire JF, Geha RS, Umetsu DT. Myocardial specific creatine phosphokinase isoenzyme elevation in children with asthma treated with intravenous isoproterenol. J Allergy Clin Immunol 1986;78(4, Part 1):631-636.
33. Fitchett DH, McNichol MW, Riordan JF. Intravenous salbutamol in management of status asthmaticus. Br Med J 1975;1:53-55.
34. Nogrady SG, Hartley JPR, Seaton A. Metabolic effects of intravenous salbutamol in the course of severe asthma. Thorax 1977;32:559-562.
35. Boe J, Carlsson L-G, Hetta L, Karlson B, Ljungholm K. Acute asthma—plasma levels and effect of terbutaline I.V. injection. Eur J Respir Dis 1985;67:261-268.
36. May CS, Paterson JW, Spiro SG, Johnson AJ. Intravenous infusion of salbutamol in the treatment of asthma. Br J Clin Pharmacol 1975;2:503-508.
37. Williams SJ, Parrish RW, Seaton A. Comparison of intravenous aminophylline and salbutamol in severe asthma. Br Med J 1975;4:685.
38. Femi-Pearse D, George WO, Ilechukwu ST, Elegbeleye OO, Afonja AO. Comparison of intravenous aminophylline and salbutamol in severe asthma. Br Med J 1977;1:491.
39. Johnson AJ, Spiro SG, Pidgeon J, Bateman S, Clark SW. Intravenous infusion of salbutamol in severe acute asthma. Br Med J 1978;1:1013-1015.
40. Lawford P, Jones BJM, Milledge JS. Comparison of intravenous and nebulised salbutamol in initial treatment of severe asthma. Br Med J 1978;1:84.
41. Moler FW, Hurwitz ME, Custer JR. Improvement in clinical asthma score and P_{aO_2} in children with severe asthma treated with continuously nebulized terbutaline. J Allergy Clin Immunol 1988;81:1101-1109.
42. Portnoy J, Aggarwal J. Continuous terbutaline nebulization for the treatment of severe exacerbations of asthma in children. Ann Allergy 1988;60:368-371.
43. Colacone A, Wolkove N, Stern E, Afilalo M, Rosenthal TM, Kreisman H. Continuous nebulization of albuterol (salbutamol) in acute asthma. Chest 1990;97:693-697.
44. Kelly HW, McWilliams BC, Katz R, Murphy S. Safety of frequent high dose nebulized terbutaline in children with acute severe asthma. Ann Allergy 1990;64(Part II):229-233.
45. Bloomfield P, Carmichael J, Petrie GR, Jewell NP, Crompton GK. Comparison of salbutamol given intravenously and by intermittent positive-pressure breathing in life-threatening asthma. Br Med J 1979;1:848-850.
46. Edmunds AT, Godfrey S. Cardiovascular response during severe acute asthma and its treatment in children. Thorax 1981;36:534-540.
47. Robertson CF, Smith F, Beck R, Levison H. Response to frequent low doses of nebulized salbutamol in acute asthma. J Pediatr 1985;106:672-674.
48. Van Renterghem D, Lamont H, Elinek W, Pauwels R, Van der Straeten M. Intravenous versus nebulized terbutaline in patients with acute severe asthma: a double-blind randomized study. Ann Allergy 1987;59:313-316.
49. Sheong B, Reynolds S, Rajan KG, Ward MJ. A comparison of intravenous with nebulized salbutamol in the treatment of acute severe asthma. Thorax 1987;42:731.
50. Rossing TH, Fanta CH, Goldstein DH, Snapper JR, McFadden ER. Emergency therapy of asthma: comparison of the acute effects of parenteral and inhaled sympathomimetics and infused aminophylline. Am Rev Respir Dis 1980;122:365-371.
51. Fanta CH, Rossing TH, McFadden ER. Emergency room treatment of asthma: relationship among therapeutic combinations, severity of obstruction and time course of response. Am J Med 1982;72:416-422.
52. Fanta CH, Rossing TH, McFadden ED. Treatment of acute asthma: is combination therapy with sympathomimetics and methylxanthines indicated? Am J Med 1986;80:5-10.
53. Siegel D, Sheppard D, Gelb A, Weinberg PF. Aminophylline increases the toxicity but not the efficacy of an inhaled beta-adrenergic in the treatment of acute exacerbations of asthma. Am Rev Respir Dis 1985;132:283-286.
54. Newhouse MT, Lam A. Management of asthma and chronic airflow limitation: are methylxanthines obsolete? Lung 1990;168(Suppl):634-641.
55. Dolovich MB, Sanchis J, Rossman C, Newhouse MT. Aerosol penetrance: a sensitive index of peripheral airways obstruction. J Appl Physiol 1976;40:468-471.
56. Ruffin RE, Montgomery JM, Newhouse MT. Site of beta-adrenergic receptors in the respiratory tract: use of fenoterol administered by two methods. Chest 1978;74:256-260.
57. Weber RW, Smith KA, Nelson HS. Aerosolized terbutaline in asthmatics: development of subsensitivity with long-term administration. J Allergy Clin Immunol 1982;70:417-422.
58. Repsher LH, Anderson JA, Bush RK, Falliers CJ, Kass F, Kemp JP, et al. Assessment of tachyphylaxis following prolonged therapy of asthma with inhaled albuterol. Chest 1984;85:34-38.

59. Kelly HW, Murphy S. Should anticholinergics be used in acute severe asthma? Ann Pharmacother 1990;24: 409-416.
60. Lam A, Newhouse MT. Management of asthma and chronic airflow limitation: are methylxanthines obsolute? Chest 1990;98:44-52.
61. Fanta CH, Rossing TH, McFadden ER Jr. Glucocorticoids in acute asthma: a critical controlled trial. Am J Med 1985;74:845-851.
62. Littenberg B, Gluck EH. A controlled trial of methyylprednisolone in the emergency treatment of acute asthma. N Engl J Med 1986;314:150-152.

Clinical Aspects of Aerosol Physics

Myrna Dolovich PEng

Introduction

Respiratory diseases can be broadly classified into those that affect the airways and those that affect the lung parenchyma, referred to as obstructive and and restrictive (or non-obstructive), respectively. Disorders in the airway diseases include reduction in airway caliber and/or alterations in surface transport, and in the parenchymal diseases, inflammation and injury to lung tissue.

Aerosols are used in the diagnosis and treatment of many of these diseases. They can be used, for example, to quantify physiologic lung parameters or to verify the relevance of a suspected sensitizing agent. In order to achieve meaningful results in clinical tests or optimal efficacy in therapy, the methods must incorporate aerosol particles of a size to target the lung region being examined or treated (Table 1). The particle size of the test aerosol is a function of the system used for generating the aerosol and of the substance or drug being aerosolized. Optimal delivery of the aerosol to the lung depends upon the inhalation technique and the pulmonary function of the recipient. These factors together determine the quantity of aerosol deposited and its distribution in the respiratory tract. Meaningful interpretation of therapeutic and diagnostic results depends upon an understanding of how these factors contribute to overall delivery.

Ms Dolovich is Assistant Clinical Professor of Medicine, McMaster University, St Joseph's Hospital, Hamilton, Ontario, Canada.

A version of this paper was presented by Ms Dolovich at the Consensus Conference on Aerosol Delivery, sponsored by the American Association for Respiratory Care, The American Respiratory Care Foundation, and the journal RESPIRATORY CARE, January 10-12, 1991, in Cancun, Mexico.

Reprints: M Dolovich PEng, Firestone Regional Chest and Allergy Unit, St Joseph's Hospital, 50 Charlton Ave East, Hamilton, Ontario L8N 4A6, Canada.

Characteristics of Aerosols

An aerosol is defined as a suspension of liquid droplets or solid particles (dust) in a gaseous medium (usually air). The size of aerosol particles is important in determining the aerosol's injurious, diagnostic, or therapeutic behavior in the lung.

Therapeutic and diagnostic aerosols are heterodisperse (that is, they consist of particles or droplets of various diameters and shapes). The distribution of the aerosol-particle diameters can be described statistically,[1] thus establishing the two parameters—the median diameter of the particles and the standard deviation of particle diameters—that characterize the overall behavior of the aerosol. These two numbers are determined from the frequency distribution curve of particle diameter versus either the particle number (or count), the surface area, or the mass (volume). If the logarithms of the diameters are plotted, the resulting curve can be the familiar bell-shaped, normal distribution curve (Fig. 1A). When the data are further graphed as a cumulative function on linear log paper, an elongated S-shaped line results (Fig. 1B). The median diameter can then be read directly at the 50% point. The geometric (for logarithmic functions) standard deviation (GSD) is related to the slope of this line, and is calculated as the ratio of the median diameter to the diameter at 15.9% or the ratio of the diameter at 84.1% to the median diameter. It is convenient to specify diameter as aerodynamic diameter because the shape of the particles within the aerosol may be irregular and the density of the drugs and formulations are varied. Use of the aerodynamic scale transforms the particle being assessed into a water droplet (density 1 g/mL) of a diameter having the same settling velocity in still air as the original particle. This standardized scale allows a comparison of the behavior of different aerosols in the lung or the external environment, regardless of their density or structure.

Table 1. Use of Aerosols in Diagnosis

Disease	Techniques	Application	Site of Deposition	Particle Size
Primary ciliary dyskinesia, bronchial disorders, lung transplants	Mucociliary clearance	Ciliary dysfunction, airway caliber, mucus production	Airway	> 3 μm
Asthma	Inhalation challenge	Airway responsiveness	Airway	1-5 μm
Interstitial lung disease, pneumocystis pneumonia, ARDS	Respiratory solute absorption	Epithelial permeability	Parenchyma	< 2 μm
Pulmonary embolism, localized airway disease, vasculitis	Ventilation/ perfusion	Vascular occlusion, surgical evaluation	Parenchyma	< 2 μm
Cystic fibrosis, asthma, respiratory syncytial virus	Dosimetry	Drug distribution/ response to therapy	Airway/parenchyma	< 5 μm

In estimating drug delivery, the median aerodynamic diameter in terms of the mass of the particles (MMAD) is usually specified. This is the diameter around which the mass is equally divided (ie, 50% of the mass resides in particles smaller than the MMAD and 50% in particles larger than the MMAD). Aerosol particles of equivalent MMAD have similar deposition in the lung irrespective of their actual size and composition.

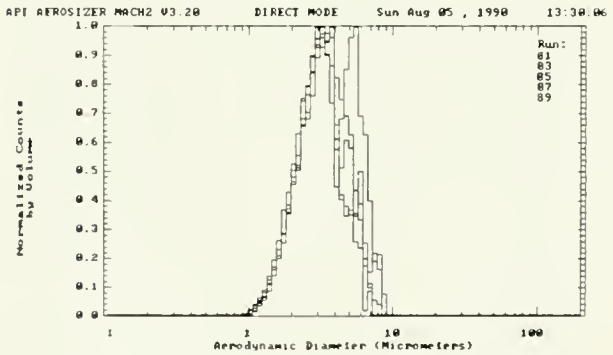


Fig. 1A. Frequency distribution plots for beclomethasone MDI (Beclovent) as measured by the Aerosizer, a laser particle-sizing system (Amherst Process Instruments, Amherst MA). Normalized frequencies in terms of volume or mass are plotted on the vertical axis against the logarithms of the aerodynamic diameters of the particles on the horizontal axis. Five separate actuations from the same MDI were sampled to illustrate the reproducibility of the size characteristics.

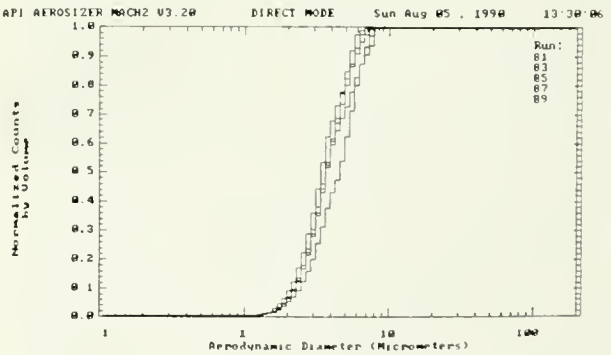


Fig. 1B. The cumulative mass distribution plots for Beclovent MDI (beclomethasone). The MMAD is 3.84 μm with a GSD of 1.46 (mean of the 5 runs).

The GSD is a measure of the variability of the particle diameters within the aerosol. A high GSD indicates a broad distribution of diameters (ie, more particles of larger and smaller diameter are present than in an aerosol of lower GSD). If the GSD of an aerosol increases, the MMAD will increase because the larger particles carry more mass.[1] This may reduce the amount of aerosol available to the patient because a greater portion of large particles is filtered out prior to inhalation, or if inhaled may deposit in the oropharynx or proximal airways.

Respirable particles are generally considered to be those with aerodynamic diameters < 5 μm. These

particles, particularly those with a 3-μm diameter, are efficiently deposited in the lower respiratory tract by sedimentation during quiet breathing.[2] It has become usual practice to state the percentage of the aerosol mass contained in particles < 5 μm, in addition to the MMAD and GSD. This number permits an assessment of the respirable dose delivered to the lung. The usefulness of this number can be seen in Figure 2, taken from an abstract reported by my group,[3] which shows these values for three aerosol systems used to deliver pentamidine. Two ultrasonic nebulizers, the Portasonic (DeVilbiss Health Care Inc) and FISONeb (Fisons Corp), generate markedly different percentages of respirable aerosol; the Respirgard II (Marquest Medical Products Inc), a jet nebulizer, produces an aerosol containing the highest percentage of droplets < 1 μm. It can be anticipated that different doses of pentamidine must be prescribed for use with these three systems to obtain equivalent delivery to the lung and a similar clinical response. The lung distribution pattern obtained from these three systems would also be expected to differ; the finer aerosol of the Respirgard II should produce a more uniform pattern with increased penetration to the peripheral airways and alveoli.[4]

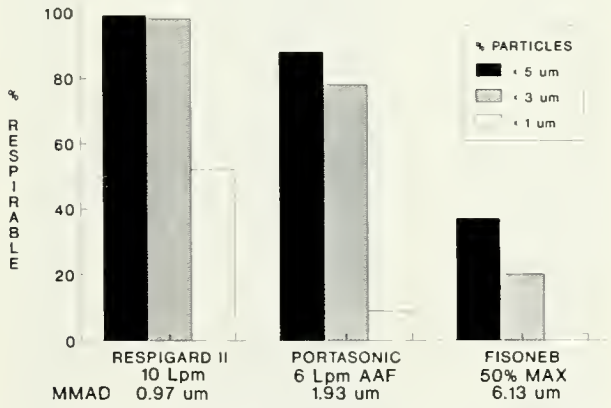


Fig. 2. Bar graphs illustrating the particle-size distribution for three nebulizer systems used to generate pentamidine aerosol under the operating conditions shown. Variability is seen in the percentage of respirable particles contained in the three aerosols from these systems.

Aerosol Deposition

Particle deposition onto surfaces in the lung depends largely upon three physical principles: (1) impaction, a function of particle inertia; (2) sedimentation due to gravity; and (3) diffusion resulting from Brownian motion of fine, submicronic (< 1 μm) particles. Electrical charges carried by particles and, in the normal unobstructed lung, simple contact or interception of particles by airway walls are mechanisms considered less important when dealing with medicinal aerosols. The diameter of the particle or droplet determines which of the three main mechanisms predominates. Limitations of the distance a particle travels due to either sedimentation or impaction is a function of the square of the particle diameter, whereas diffusion distance is determined by the inverse square root of particle diameter. The distance a particle travels before deposition due to either sedimentation or impaction *decreases* in proportion to *increases* in the square of the particle diameter, whereas diffusion distance *increases* in proportion to *decreases* in the square root of particle diameter.

Due to the geometry of the lung, particles < 10 μm deposit in the respiratory tract; the distribution between the various regions is a function of particle diameter, breathing pattern, and airway diameter.[2] Equations predicting deposition efficiency for both nose and mouth breathing are described in the literature, and there appears to be good agreement between theoretical and experimental data.[3] Deposition due to inertial impaction in the oropharyngeal area and large airways is predominant for particles > 5 μm, even with normal tidal breathing. Particles < 5 μm, considered respirable, are influenced mainly by gravity, and in the normal lungs deposit preferentially in the periphery. Deposition of submicronic particles, approximately 0.5 μm and smaller, is increased by diffusion throughout the alveolar region. Increased particle velocity resulting from changes in airflow dynamics or inhalation of particles of greater density causes increased deposition by impaction and sedimentation. Aerosol deposition can be further augmented by prolonging the residence time of the particles in the lung, thus allowing greater time for sedimentation and diffusion.

Other factors that alter the normal distribution of particles in the lung include the hygroscopicity of therapeutic aerosols (which results in increased particle size), the pattern of breathing used to inhale the aerosol, biologic variations in airway caliber,

Table 2. Factors Affecting Deposition of Aerosols in the Lung

Physical
Particle diameter
Particle shape
Particle or formulation density
Heterodispersity
Ventilatory
Tidal volume
Inspiratory flowrate
Breath-hold time
Breathing frequency
Nose vs mouth breathing
Humidity
Anatomic
Airway caliber
Distortion due to disease

and the extent of airway narrowing due to disease (Table 2).

Hygroscopicity

Therapeutic aerosols are hygroscopic and grow two- to threefold almost instantaneously once they are inhaled into the humid airways.[5] The rate of growth to equilibrium size depends mainly upon the initial diameter and residence time in the lung. Small particles (< 3 μm) can achieve their final size within the inspiratory time of a normal breathing cycle. This increased growth results in an increased total deposition, with a shift within the lung compartments reflecting the more proximal deposition of larger particles. Clumping of powders within their delivery systems due to high humidity can reduce the amount of respirable drug available to the patient. It has been suggested that this may partially explain the observation that 400 μg of salbutamol powder is required to produce the same bronchodilator response as 200 μg of salbutamol from a metered dose inhaler (MDI).[6]

Ventilatory Factors

The pattern of breathing, in particular the inspiratory flowrate, influences the aerosol dose delivered and the distribution of that dose within the lung (Fig. 3). Increased deposition in large central airways by impaction occurs not only with an increase in particle size but also with high inspiratory flowrates (> 1 L/s).[7,8] This combination of factors results in poor delivery to the peripheral lung. A lower inspiratory flowrate (< 1 L/s) results in a greater lung dose of drug, and this can be shown to produce a better clinical response.[9] The volume of air inhaled does not appear to be as important a determinant of deposition, although a low inspiratory volume combined with a rapid inspiratory flowrate (such as in a crying infant) reduces lung delivery.[10] Particles may penetrate further into the lung in association with an increased inspiratory volume, but an enhanced clinical response does not necessarily result. If the dose is delivered at residual volume or total lung capacity and not followed by an inspiratory breath, the response is suboptimal.[11] Breath-holding for at least 10 seconds at end-inspiration increases the length of time the particles reside in the lung and, thus,

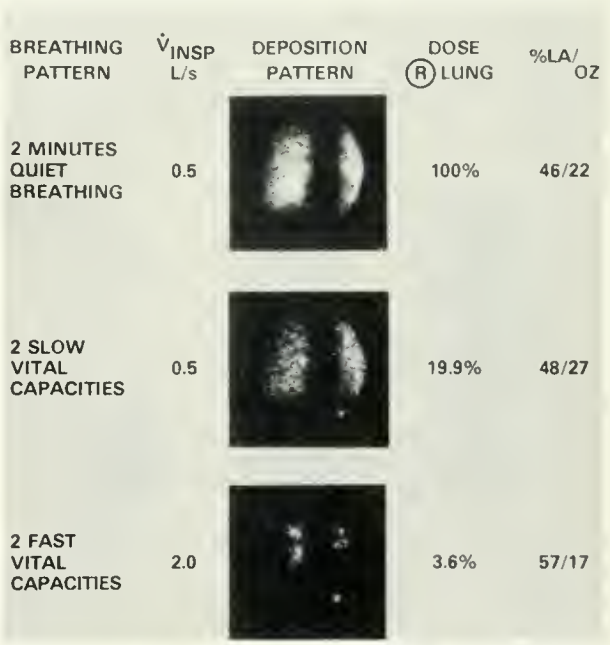


Fig. 3. Scintigraphs illustrating effect of varying inspiratory flowrate on dose and distribution of a 4.3 μm MMAD aerosol in the lung. %LA/OZ is the ratio of right (R) lung dose deposited in the large airways (LA) to that in the outer zone (OZ), a 2.5-cm strip 1-inch around periphery of lung. Distribution of aerosol in the lung, but not dose deposited, was similar for similar V_{insp}. Increasing V_{insp} by decreasing from 8 seconds to 2 seconds the time to take a vital capacity breath resulted in a much lower lung dose, with relatively more aerosol deposited in LA and less in OZ. (Reprinted, with permission, from Reference 7.)

the probability of deposition. The use of a breath-hold has been shown to enhance the response to bronchodilator aerosol, particularly if the drug is inhaled at a low flowrate.[11]

High inspiratory flowrates reduce lung delivery from inhalation of wet or pressurized aerosols but not dry powder aerosols. Because of their design, some dry powder inhalers function better when the powder is inhaled using high inspiratory flowrates.[12] For example, both the Spinhaler (Fisons) and the Rotahaler (Glaxo) require the patient to inhale the powder with flowrates of at least 100 L/min in order to successfully dispense drug.[12,13] At these high flowrates, deposition is likely to be mainly in the oropharynx and central airways.[14] The influence of this central deposition pattern on the therapeutic response is unknown. During an exacerbation of asthma, these flows may be difficult to achieve,[13] and as a result, clinical responses may be suboptimal. Newer designs of powder inhalers such as the multidose Turbuhaler (Astra Pharmaceuticals Inc)[15] and the Inhalet (Boehringer Ingelheim) require at least 60 L/min to produce optimal response; however, patients can derive some benefit from these devices with inspiratory flowrates as low as 30 L/min.[16]

Airway Caliber

Reduction in airway caliber due to increased mucus production, bronchoconstriction, or edema, or distortion of the airways due to disease alter aerosol deposition.[17,18] To a lesser degree, similar effects result from the normal interindividual variability in airway size; in normal adults, variability in deposition has been shown to correlate with the expiratory reserve volume. Deposition predictor models for the developing lung indicate that children under 5 years of age have greater airway and less pulmonary deposition than older children and adults, reflecting both the increased respiratory rate of young children and the smaller number of mature alveoli in the immature lung.[19]

Decreases in airway caliber in patients with obstructive airways disease and in asymptomatic smokers have been shown to result in central-airway deposition patterns[20] that correlate well with pulmonary function measurements.[20-22] As the FEV_1 decreases, less aerosol penetrates to the lung periphery, and a central, patchy deposition pattern is produced, reflecting impaction of aerosol particles at points of airway narrowing and deposition due to increased turbulence (Fig. 4). The amount of aerosol being deposited in the airways has been shown to increase with severity of disease, and appears to be somewhat independent of inspiratory flowrates.[23]

Fig. 4. Lung scan obtained in a patient with COPD with FEV_1 0.67 L, illustrating reduced ventilation to the lung periphery. Hot spots indicate impaction of aerosol particles at points of airway narrowing.

Aerosol Generation

Therapeutic aerosols are produced by jet and ultrasonic nebulizers, powder inhalers, and chlorofluorocarbon-containing (Freon) pressurized canisters, and can be delivered to the airways through mouthpieces, face masks, tubing, spacer devices (or holding chambers), and ventilator circuits. If the MMAD of the aerosol is initially too large, with the potential for insufficient delivery

to the lower respiratory tract or poor penetration to the lung periphery, the particle size of the aerosol can be reduced by heating, baffling, or using spacer devices that cause large particles to rainout through impaction or sedimentation.[24,25] In a valved spacer device used with a volatile aerosol, the aerosol may be further aged by allowing it to evaporate over a finite time prior to inhalation. Use of these devices yields a reduced oropharyngeal dose and hence a lower incidence of side effects, such as thrush and hoarseness from steroid aerosols.[26] A study by my group[27] suggests that use of valved devices may also produce a more uniform distribution of aerosol within the lung reflecting the reduced MMAD of the available aerosol. Newman et al[28] have shown that an increased deposition of aerosol in the lower respiratory tract can be achieved with the large (750 mL) devices, but the work of König et al[29] suggests that the large devices provide no advantage in terms of clinical responses compared to use of smaller valved spacers.

A decrease in particle size can be achieved when delivery is to mechanically ventilated patients via an endotracheal tube. Although losses occur in the tracheal tube due to its narrow diameter, sufficient respirable aerosol is created to provide adequate dosing to the lung.[30] A submicronic primary aerosol delivered in this way may produce greater lung deposition than an aerosol with a MMAD of approximately 3 μm.[31,32]

Techniques and Assessment for Drug Delivery and Response

A number of in-vivo techniques have been developed for quantitating the amount of therapeutic aerosol delivered to the lung. These include measurements of pharmacokinetics; drug loss; direct labeling of bronchodilator, replacement particles, or droplets; the use of activated charcoal to absorb the drug; and the mixing of a radiotracer with the drug for inhalation. When performing these experiments, it is important to aerosolize the drug with the tracer because the characteristics of the drug-plus-tracer aerosol are different from the tracer-only aerosol. The radioactivity can be detected by multiple probes, gamma camera, whole-body scanners, or tomographic systems, and the methodologies for using this equipment are well described in the literature.[33,34] Studies of drug deposition have been performed mainly in adults; few data are available in children.

The relevant criteria of effectiveness of therapeutic aerosols address the clinical efficacy. Responses to treatment can be assessed by a variety of outcome measurements (Table 3). The use of inhaled steroid for 1 year, for example, has been shown to result in an improvement in asthma, demonstrated by a clinical scoring system and the measurement of methacholine airway responsiveness.[35] Decreases in the numbers of inflammatory cells in bronchoalveolar lavage fluid have been observed after a short course of the steroid budesonide inhaled from an MDI.[36]

Table 3. Assessment of Responses to Inhalant Treatment

Symptom and medication scoring
Pulmonary function
Non-specific airway responsiveness
Mucociliary clearance
Respiratory epithelial clearance (small solute-DTPA)
Bronchoalveolar lavage (cells, markers)
Sputum cytology

Conclusions

Aerosols offer many advantages over alternative forms of therapy. However, the successful use of aerosols in diagnosis and treatment depends upon an understanding of the principles of aerosol generation and factors affecting delivery. In general, inhalation of small particles (< 3 μm) using a low flowrate (< 1 L/s) and followed with a 10-second breath-hold at end-inspiration will enhance lower respiratory tract deposition and provide good clinical response.

ACKNOWLEDGMENTS

I thank Mrs Maureen McPhail for her secretarial assistance in typing the manuscript.

REFERENCES

1. Morrow PE. Conference on the scientific basis of respiratory therapy: aerosol therapy. Aerosol characterization and deposition. Am Rev Respir Dis 1974;110(6, Part 2):88-99.

2. Yu CP, Nicolaides P, Soong TT. Effect of random airway sizes on aerosol deposition. Am Ind Hyg Assoc J 1979;40:999-1005.
3. Dolovich M, Chambers C, Newhouse M. Characterization of three systems used to deliver pentamidine (P) aerosol (abstract). Am Rev Respir Dis 1990;141(4, Part 2):A153.
4. Howite JS, Baskin MI, Sheetz MS, Abd AG. Comparison of the delivered dose and regional distribution of aerosolized pentamidine using different delivery systems (abstract). Am Rev Respir Dis 1990;141(4, Part 2):A53.
5. Morrow PE. Factors determining hygroscopic aerosol deposition in airways. Physiol Rev 1986;66:330-375.
6. Martin GP, Bell AE, Marriott C. An in vitro method for assessing particle deposition from metered pressurized aerosols and dry powder inhalers. Int J Pharm 1988;44:57-63.
7. Ryan G, Dolovich MB, Obminski G, Cockcroft DW, Juniper E, Hargreave FE, et al. Standardisation of inhalation provocation tests: influence of nebulizer output, particle size and method of inhalation. J Allergy Clin Immunol 1981;67:156-161.
8. Dolovich MB, Ruffin RE, Roberts RS, Newhouse MT. Optimal delivery of aerosols from metered dose inhalers. Chest 1981;83:911-915.
9. Newman SP, Pavia D, Clarke SW. How should pressurized beta-adrenergic bronchodilator be inhaled? Eur J Respir Dis 1981;62:3-21.
10. Murakami G, Igarashi T, Adachi Y, Matsuno M, Adachi Y, Sawai M, et al. Measurement of bronchial hyperreactivity in infants and preschool children using a new method. Ann Allergy 1990;64:383-387.
11. Newman SP, Bateman JRM, Pavia D, Clarke SW. The importance of breath-holding following the inhalation of pressurized aerosol bronchodilators. In: Baran D, ed. Recent advances in aerosol therapy: first Belgian symposium on aerosols in medicine. Brussels: UCB Pharmaceuticals, 1979:117-122.
12. Auty RM, Brown K, Neale MG, Snashall PD. Respiratory tract deposition of sodium cromoglycate is highly dependent upon technique of inhalation using the Spinhaler. Br J Dis Chest 1987;81:371-380.
13. Pedersen S. How to use a Rotahaler. Arch Dis Child 1986;61:11-14.
14. Vidgren M, Paronen P, Vidgren P, Vainio P, Nuutinen J. In-vivo evaluation of the new multiple dose powder inhaler and Rotahaler using gamma seintigraphy. Acta Pharm Nord 1990;1:3-10.
15. Persson G, Gruvstad E, Stahl E. A new multiple dose powder inhaler (Turbuhaler) compared with a pressurized inhaler in a study of terbutaline in asthmatics. Eur Respir J 1988;1:681-684.
16. Dolovich M, Vanzieleghem M, Hidinger K-G, Newhouse MT. Influence of inspiratory flow rate on the response to terbutaline sulphate inhaled via the Turbuhaler (abstract). Am Rev Respir Dis 1988;137(4, Part 2):433.
17. Santolicandro A, Ruschi S, Fornai E, Giuntini C. Imaging of ventilation in chronic obstructive pulmonary disease. J Thorac Imag 1986;1:36-53.
18. Monrigal JP, Granry JC, Vilayleck S, Lejeune JJ, Chavellat M. Effects of the endotracheal state on the progression of antibiotics administered by aerosol route (abstract). Am Rev Respir Dis 1990;141(4, Part 2):A525.
19. Xu JB, Yu CP. The effects of age on deposition of inhaled aerosols in the human lung. Aerosol Sci Technol 1986;5:349-357.
20. Dolovich MB, Sanchis J, Rossman C, Newhouse MT. Aerosol penetrance: a sensitive index of peripheral airways obstruction. J Appl Physiol 1976;40:468-471.
21. Howite JS, Gorvoy JD, Smaldone GC. Quantitative deposition of aerosolized gentamicin in cystic fibrosis. Am Rev Respir Dis 1987;136:1445-1449.
22. Kim CS, Lewars GA, Sackner MA. Measurement of total lung aerosol deposition as an index of lung abnormality. J Appl Physiol 1988;64:1527-1536.
23. Chan TL, Lippmann M. Experimental measurement and empirical modelling of the regional deposition of inhaled particles in humans. Am Ind Hyg Assoc J 1980;41:399-409.
24. Dolovich M. Physical principles underlying aerosol therapy. J Aerosol Med 1989;2:171-186.
25. O'Doherty MJ, Thomas SH, Page CJ, Bradbeer C, Nunan TO, Bateman NT. Does inhalation of pentamidine in the supine position increase deposition in the upper part of the lung? Chest 1990;97:1343-1348.
26. Salzman GS, Pyszczynski DR. Oral pharyngeal candidiasis in patients treated with beclomethasone dipropionate delivered by metered-dose inhaler alone and with Aerochamber. J Allergy Clin Immunol 1988;81:424-428.
27. Dolovich M, Ruffin R, Corr D, Newhouse M. Clinical evaluation of a simple demand inhalation MDI aerosol delivery device. Chest 1983;84:36-44.
28. Newman SP, Millar AB, Lennard-Jones TR, Morén F, Clarke SW. Improvement of pressurized aerosol deposition with Nebuhaler spacer device. Thorax 1984;39:935-941.
29. König P, Gayer D, Kantak A, Kreutz C, Douglass B, Hordvik NL. A trial of metaproterenol by metered-dose inhaler and two spacers in preschool asthmatics. Pediatr Pulmonol 1988;5:247-251.
30. Fuller HD, Dolovich MB, Posmituck G, Wong Pack W, Newhouse MT. Pressurized aerosol versus jet aerosol delivery to mechanically ventilated patients: comparison of dose to the lungs. Am Rev Respir Dis 1990;141:440-444.
31. Flavin M, MacDonald M, Dolovich M, Coates G, O'Brodovich H. Aerosol delivery to the lung with an infant ventilator. Pediatr Pulmonol 1986;2:36-39.
32. MacIntyre NR, Silver RM, Miller CW, Schuler F, Coleman RE. Aerosol delivery in intubated, mechanically ventilated patients. Crit Care Med 1985;13:81-84.

33. Dolovich M. Lung deposition of aerosols: methods and assessments. In: Epstein SW, ed. Metered dose inhalers. Proceedings of an international workshop. Mississauga, Canada: Astra Pharmaceuticals, 1984:27-37.
34. Brain JD, Valberg PA. Deposition of aerosols in the respiratory tract. Am Rev Respir Dis 1979;120:1325-1373.
35. Juniper EF, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in non-steroid-dependent asthmatics. Am Rev Respir Dis 1990;142:832-836.
36. Howarth PH, Djukanovic R, Wilson J, Wilson S, Britten K, Roche W, et al. Airway inflammation and asthma: the influence of inhaled beclomethasone dipropionate. Clin Exp Allergy 1990;20(1, Suppl):94.

Aerosol Generators and Delivery Systems

Stephen P Newman PhD FInstP

Introduction

Although inhalation therapy has been practised for many centuries, its modern era can probably be dated to the 1930s when adrenaline was first given by hand-held squeeze-bulb nebuliser for the treatment of asthma.[1] Subsequently, inhalation therapy was revolutionized by the introduction, in 1956, of the pressurized metered dose inhaler (MDI), which has remained a cornerstone of asthma therapy during the ensuing decades. Today, the respiratory physician can choose from a range of inhalation devices. Pressurized MDIs may be used either alone or in conjunction with a spacer or holding chamber, while both single-dose and multidose powder inhalers are useful alternatives. Nebulisers continue to be used, but squeeze-bulb devices have been largely superseded by either gas-driven 'jet' or ultrasonic nebulisers.

Each device has its advantages and disadvantages and, hence, its own clinical roles to play. In this paper, I will compare and contrast the different devices in terms of their output characteristics, deposition efficiencies, and practical aspects.

Dr Newman was Principal Physicist and Honorary Senior Lecturer, Department of Thoracic Medicine, Royal Free Hospital and School of Medicine, London, United Kingdom when this paper was written. He is now associated with Pharmaceutical Profiles Ltd, Nottingham, United Kingdom.

A version of this paper was presented by Dr Newman during the Consensus Conference on Aerosol Delivery, sponsored by the American Association for Respiratory Care, the American Respiratory Care Foundation, and the journal RESPIRATORY CARE, January 10-12, 1991, in Cancun, Mexico.

Reprints: Stephen P Newman, Pharmaceutical Profiles Ltd, 2 Faraday Building, Highfields Science Park, University Blvd, Nottingham NG7 2QP, United Kingdom.

Nebulisers

Jet vs Ultrasonic Nebulisers

Nebulisers are of two types (jet and ultrasonic), each functioning by a different principle.[2,3] Jet nebulisers (Fig. 1) utilise the Bernoulli principle. Compressed gas from a domiciliary compressor, air or oxygen cylinder, or hospital air line is passed through a narrow constriction known as a venturi. This creates an area of low pressure, and drug solution from a reservoir is thus drawn up a feed tube and is fragmented into droplets by the air stream. Only the smallest droplets leave the nebuliser directly, while the majority impact on baffles and walls, and are returned to the reservoir. Consequently, nebulisation takes several minutes to complete, depending upon the initial volume. A substantial proportion of the dose is retained permanently (as a dead or residual volume) on baffles and the internal walls of the nebuliser chamber, and cannot be released. Droplet mass median aerodynamic diameter (MMAD) and nebulisation time to dryness (until no more aerosol is produced) are both inversely proportional to pressure upstream of, and compressed gas flowrate through, the nebuliser.

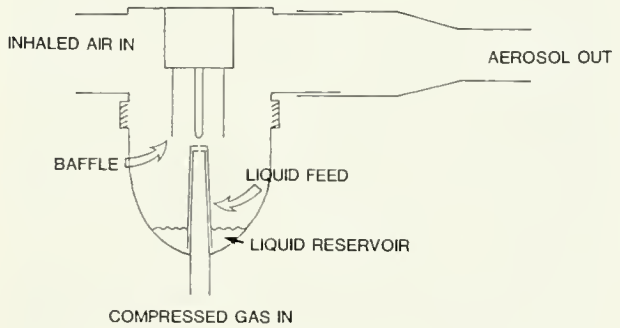


Fig. 1. Design of typical jet nebuliser.

In the ultrasonic nebuliser, a high-frequency signal (typically about 1 MHz) is used to create a fountain of droplets above a liquid reservoir, with the largest

of these impacting on baffles and the internal walls. There has been concern that sonification may damage some drug molecules.[4] Droplet MMAD is inversely related to the ultrasonic frequency, although this frequency can seldom be varied by the user. Drug output rate is proportional to the power setting or amplitude of the ultrasonic signal.

Ultrasonic nebulisers have a tendency to have a larger droplet size and a higher output rate in mL/min (and hence a shorter nebulisation time to dryness) than jet nebulisers. Some ultrasonic nebulisers with a frequency much less than 1 MHz have a droplet MMAD > 15 μm.[5] Jet nebuliser aerosols cause less cough and irritation than ultrasonic nebuliser aerosols,[6] but the reason for this is unclear. Large volume models of both jet and ultrasonic nebuliser are available for continuous delivery of aerosol over periods of many hours: of these, the Collison nebuliser is probably best known.[7] The drug solution within the nebuliser will become increasingly concentrated with time because of preferential evaporation of diluent. This effect is related to humidity, and is most marked in the jet nebuliser when the driving gas is dry air from a cylinder.[8]

Desirable Output Characteristics

It is often assumed that all nebulisers are essentially similar in performance, and it is the tendency in clinical practice for the nearest nebuliser to be taken from the shelf when one is needed, without consideration of its output characteristics.[9,10] Surveys of nebuliser apparatus have shown marked differences in the drug output, droplet size, and nebulisation time from various nebuliser systems, and in the pressures and flowrates generated by various domiciliary compressors.[11-14] Hence, in clinical practice there may be a wide variation in the quality and quantity of aerosol that the patient receives, depending upon the apparatus selected (Table 1).

Laboratory studies have predicted that there can be a 10-fold variation in respirable dose, depending upon the choice of nebuliser, its volume fill, and the compressed gas flowrate.[13] Additionally, high batch-to-batch and within-batch variation in output characteristics among allegedly identical nebulisers have been reported.[15,16]

Table 1. Comparison of Some Technical Aspects of Various Jet Nebuliser and Compressor Systems Available in 1990 in the United Kingdom

Sound level	50-67 db
Weight	2.1-4.1 kg
Static pressure	95-452 kPa
Free flow	7.0-12.2 L/min
Dynamic (in-line) flow	3.6-6.9 L/min
Output in 10 min	30-67% of 2.5 mL 17-44% of 5 mL
Percent of mass < 5 μm	16-62%
Cost	£65-£145, minus sales tax $106-$237, minus sales tax

Ideally, a nebuliser system should have a high drug output (mass of drug released as aerosol) plus low residual volume, a small droplet size for penetration into the lungs (MMAD < 5 μm) and a short nebulisation time for patient compliance. A relatively powerful compressor, capable of producing an in-line flowrate through a nebuliser of at least 8 L/min, will reduce droplet size and nebulisation time. Two such compressors available in the United Kingdom are the Maxi III and CR 60.* When coupled to certain brands of nebuliser (eg, DeVilbiss 646, Cirrus, and Turret), the ideals described above are met reasonably well, although they are to some extent mutually incompatible, and compromise is necessary. For instance, nebulisers deliver more drug as aerosol with a 4-mL volume fill than with a 2 mL-volume fill,[13] even if the extra 2 mL is composed entirely of diluent. Conversely, nebulisation time is halved with a 2-mL fill, and many jet nebulisers will have aerosolized the majority of this dose in the acceptably short time of 5 minutes[17] depending upon the compressed gas flowrate. Nebulisers may be improved by changes in design,[18] for instance reducing the dead volume by means of plastic inserts placed in the nebuliser chamber.

In conventional nebulisers, almost all the dose produced during exhalation is wasted to the atmosphere. A hand-operated triggering mechanism, intended to synchronize aerosol production with inhalation, will partly overcome this problem, but at the expense of increasing nebulisation time to

*Suppliers are identified in the Product Sources section at the end of the text.

dryness. Drug delivery is significantly enhanced by the use of a valved storage chamber (eg, Mizer) to hold aerosol generated during exhalation.[19] Even the addition of a simple 50-mL tube to a nebuliser as an expiratory reservoir improves drug delivery.[20] Although such devices may significantly increase the bulk of the nebuliser system, they enable a given amount of drug to be delivered in a shorter time (which may enhance compliance), and should produce important financial savings for expensive drugs.

Deposition Efficacy

The technical factors listed in Table 2, together with patient-related factors, will determine the site and extent of aerosol deposition in the lung, which should in turn be a major determinant of clinical efficacy.

Table 2. Technical and Patient-Related Factors that Determine the Pattern of Aerosol Deposition, the Major Determinant of Clinical Efficacy

Technical Factors	
Type of nebuliser Individual nebuliser Flowrate & compressor (jet nebuliser) Frequency & amplitude (ultrasonic nebuliser) Volume fill Drug concentration effect Auxiliary tubing and baffles Auxiliary vents Triggering devices Storage chambers Solution viscosity & surface tension Humidity & temperature	Drug output & dead volume Droplet size spectrum Nebulisation time to dryness
↓	
Patient-Related Factors	
Breathing pattern Mouth or nose breathing Airway geometry Health or disease Airway obstruction Posture Intermittent positive pressure	Total and regional aerosol deposition
↓	
	Clinical efficacy

The percentage of the dose placed in a nebuliser that is delivered to the lungs can be as low as 1%[21] and as high as 30% in the occasional individual.[22] This reflects not only intersubject variability in deposition but also the use of different nebuliser systems and operating conditions. Some ultrasonic devices with MMADs > 15 μm in diameter will deposit negligible aerosol in the lungs.[5] In a recent study, we found means of 9.3% and 3.1% of the dose deposited in the lungs from two commercially available jet nebuliser systems with MMADs of 3.3 μm and 7.7 μm.[23] Inherently low deposition from nebulisers is to be expected because of (1) retention of approximately half the initial solution volume on the internal walls, (2) increase in the concentration of this solution during nebulisation, so that the majority of the dose is retained in the apparatus, (3) loss of aerosol generated during the exhalation phase of breathing, (4) termination of treatment prior to nebulisation to dryness, (5) deposition of inappropriately large droplets (> 5 μm) in the oropharynx, and (6) exhalation of many smaller droplets.

Selective deposition in the most peripheral parts of the lungs can be achieved by conventional nebulisers fitted with auxiliary baffles downstream of the nebuliser chamber;[24,25] however, total lung deposition from such systems (eg, Respirgard II) may be less than that from conventional devices because not only most of the nonrespirable aerosol but also some of the respirable aerosol is removed by the baffles.

Only a mean 2.9% of a nebulised dose was recorded in the lungs of 7 stable, intubated, mechanically ventilated patients, compared to a mean of 11.9% in 3 healthy nonventilated subjects.[26] Impaction within the tube itself probably accounted at least in part for the reduced deposition in the intubated patients; major losses of aerosol on tubing between the nebuliser and the point of outlet have been noted in vitro.[27] Deposition following delivery via endotracheal tubes will depend upon many factors, including the aerosol droplet size, the breathing pattern, the diameter of the tubing,[27] the positioning of the nebuliser in the ventilator circuit,[28] and the way in which aerosol release is synchronized with inhalation.[29]

Although the deposition pattern can be altered by artificial breathing manoeuvres,[30,31] tidal

breathing is normally used in the clinical situation. The addition of deep breathing[32,33] and breath-holding[33] during nebuliser therapy did not augment the deposition achieved by tidal breathing. Either a mouthpiece or face mask can be used, although upper-airway losses should be relatively high and lung deposition relatively low for the latter because the nose is a very efficient aerosol filter.[34] The addition of intermittent positive-pressure breathing (IPPB) to nebuliser therapy does not improve deposition,[35] partly explaining why this modality is no longer recommended other than for patients requiring assisted ventilation.[36] The addition of oral high-frequency oscillation (OHFO) to nebuliser therapy produces a complex, but essentially negative, effect on aerosol delivery.[37] Inhalation in the supine position may improve upper-lung-zone deposition during pentamidine aerosol therapy.[38]

The manner in which the patient's inhalation may affect aerosol deposition, either directly, or indirectly via manipulation of the nebuliser output characteristics, is still not completely understood.[39,40] Deposition of drug may be related to minute ventilation,[41,42] and the low deposition values achieved in infants[34] may arise partly because their minute ventilation is substantially less than the compressed gas flowrate (in liters per minute) supplied to a jet nebuliser. Because aerosol is only carried into the lung during inhalation, deposition may be especially low in severely dyspneic patients who inhale by rapid shallow breaths, and large doses may have to be delivered in such patients in order to compensate for the effects of this pattern.

Clinical Efficacy

Because major differences exist in output characteristics and in aerosol deposition among different systems, this should also be reflected in differences in clinical efficacy. Yet, it has proved difficult to demonstrate changes in bronchodilator response among different nebulisers or for the same nebuliser operated at different compressed gas flowrates, and hence with different droplet sizes.[43,44] However, this probably reflects the high bronchodilator doses (at least 1 mg) used in these studies, which are typical of those occurring in clinical practice. Such doses may be effective even from a relatively inefficient nebuliser system. Differences in bronchodilator responses between nebulisers can be shown in stable asthmatics when smaller doses are used.[23]

Choice of nebuliser may assume much greater importance when drug substances other than bronchodilators are used (for instance, to minimize oropharyngeal deposition and hence systemic delivery of topical suspensions of corticosteroids or to ensure efficient delivery of expensive drug substances). Use of a specific brand of nebuliser is also important for standardizing bronchial provocation tests.[30] Only certain nebulisers with a MMAD < 2 μm are appropriate for selective drug targeting of alveolar regions. Drugs that may require such nebulisers include pentamidine,[24] anti-viral agents,[45] alpha$_1$-antitrypsin,[46] and substances for systemic absorption.[47] In addition to nebulisers with auxiliary baffles mentioned previously, such as the Respirgard II,[24] devices originally designed for lung ventilation scanning such as Cadema and Ultravent (formerly known as Syntevent) and the SPAG-2 Collison nebulizer[46] may be especially appropriate in these circumstances.[48] Such devices may also reduce losses in endotracheal tubes, and may hence improve drug delivery to mechanically ventilated patients.[27]

Advantages and Disadvantages

The simplicity of inhalation technique (tidal breathing) from a nebuliser is one of its greatest merits, although even this may be a problem in severely dyspneic patients.[49] Hence nebulisers can be used in situations where other devices might be unsuitable (for instance, by infants less than one year,[50] and for other groups of patients who cannot use other devices successfully). Nebulisers can be incorporated into ventilator circuits,[51] although here they are rather inefficient as previously discussed. Oxygen may be used as a driving source in jet nebulisers, where appropriate. Virtually any drug solution or suspension can be nebulized and in virtually any dose. For instance the aerosolization of large doses of antibiotic solutions (up to 1 g) for the prophylaxis of pseudomonas infection in cystic fibrosis would be impossible using any other device.[52] The types of drug substances delivered by nebuliser are certain to increase in the future.

Conversely, nebulisers also have some serious drawbacks. Treatment is slow (over several minutes), and the compressor or ultrasonic generator is relatively expensive, bulky, and not portable. Electricity is generally required. Although it is easy to put unusual drug substances in nebulisers, it is also easy to contaminate nebuliser solutions, especially when multidose vials are used. Hypotonic and hypertonic solutions, and preservatives, may cause bronchoconstriction,[53,54] and it should be borne in mind that the tonicity of solutions increases with time owing to evaporation of diluent.

Unlike other inhalation devices, nebuliser systems are usually not supplied with the drugs that go in them, and hence it is not generally necessary to satisfy drug regulatory authorities about the output characteristics of nebulisers. There appears to be poorer control over the performance of nebulisers than over that of other devices. I have observed that manufacturers persist in providing misleading information about the droplet size of nebulisers (for instance, quoting droplet size by number and not by volume or mass, which automatically makes a heterodisperse aerosol from a nebuliser look smaller than it really is) and about the power of compressors (stating only the maximum 'static' pressure and maximum 'free' flow, rather than the lower pressures and flows that pertain when nebuliser and compressor are actually connected).

There has been concern over the recent increase in demand for home nebuliser therapy,[55] and surveys have revealed a lack of supervision and poor knowledge of the correct action to take during acute exacerbations of asthma.[10,56]

Pressurized Metered Dose Inhaler

Drug Delivery

Pressurized MDIs comprise the drug, usually as micronized crystals, suspended with a surfactant in a mixture of two or three chlorofluorocarbon (CFC) propellants. The metered volume ranges from 25 to 100 μL, and contains 50 μg to 5 mg of drug substance.[57,58] The propellant vapor pressure varies from approximately 300 to 500 kPa at 20°C, depending upon the propellant mixture. Spray characteristics will depend upon a range of physicochemical factors listed in Table 3. Because the canister is pressurized, the spray moves rapidly and directionally, and the majority of the dose is deposited in the oropharynx,[59-63] with a percentage deposited in the lungs that has been estimated variously to average between 10 and 25%. There is a high intersubject variability in lung deposition. The high oropharyngeal deposition may, in the case of topical corticosteroids, lead to local side effects.[64]

Table 3. Factors Determining Drug Delivery from Pressurized Metered Dose Inhalers

Physicochemical Factors
Propellant vapour pressure
Metered volume
Mass of drug per metered dose
Drug concentration
Surfactant concentration
Ethanol and other additives
Drug particle size
Temperature and humidity
Actuator-orifice dimensions
Mode of Inhalation
Coordination of actuation
'Cold-Freon' problems
Slow, deep inhalation
Breath-holding pause?
Closed- vs open-mouth technique?
Shake inhaler to disperse drug?
Hold inhaler upright to refill?
Instruction on technique
Spacer Devices
Type of spacer
MDI-spacer combination
Mode of inhalation
Other Auxiliary Devices
Breath-actuated MDI (Autohaler)
GentleHaler
Training Aids

Successful drug delivery from an MDI depends critically on inhalation technique (Table 3). The MDI should be actuated during a slow, deep inhalation, with a 10-second breath-hold following.[65] Patients are usually advised to place the mouthpiece between closed lips,[65] although holding the mouthpiece a few centimeters from the open mouth is sometimes recommended.[60] Coordination between actuating the MDI and inhaling is crucial. Many patients cannot do this: yet, drug delivery and efficacy are negligible if the MDI is fired after inhalation has been completed

(ie, the entire dose impacts in the oropharynx).[66] Other patients stop inhaling when the cold blast of the propellants hits the back of the throat (the so-called 'cold-Freon' effect). Predictably, these problems are especially troublesome in children and in the elderly. Patients with imperfect technique are often unaware that their poor technique produces a suboptimal effect.[67] Many patients who have acquired good inhaler technique will lose it with continued treatment.

A breath-actuated pressurized MDI (Autohaler) was introduced in the United Kingdom in 1989 for delivery of albuterol and more recently for cromolyn sodium.[68] This device neatly overcomes coordination difficulties, but presumably will not help to solve cold-Freon problems. However, there is evidence that patients can learn to use this device more easily than a conventional pressurized MDI.[68] Correct instruction and repeated checking of technique are essential, and the use of training aids may help in this.[69-71] A new pressurized device that delivers a slow-moving spray (GentleHaler) has been described,[72] which may help to reduce problems of poor coordination and cold-Freon difficulties, and which may reduce oropharyngeal deposition of inhaled corticosteroids.

Advantages and Disadvantages

The pressurized MDI has some superb practical advantages that explain its popularity over several decades. It is cheap, quick to use, small, portable, multidose, and does not need electricity. The contents are sealed and cannot be contaminated.

Conversely, the pressurized MDI also has some serious limitations. Because the required inhalation technique is difficult to master, the device is unsuitable for some groups of patients (eg, the very young and for many other individuals).[73] Only a limited range of drugs is available by MDI, and it is difficult to deliver high doses conveniently. CFC propellants are required, but these are likely to be banned worldwide because of their contribution to ozone depletion and to global warming. Alternative propellants must be sought.[74] As discussed above, propellants are responsible for one of the major forms of pressurized MDI misuse and may cause bronchoconstriction in some asthmatic subjects.[75]

Spacers and Chambers

It is not widely known that the first pressurized MDI produced by Riker Laboratories in 1956 had an elongated tube-shaped mouthpiece, which was shortened to its present length about 2 years later. A variety of spacer tubes and chamber devices to be attached to the MDI mouthpiece are available, and many prototype devices and homemade spacers or chambers have been described. Valved spacer devices (such as Nebuhaler, Volumatic, Aerochamber, and Rondo) and collapsible spacers (such as InspirEase and AeroVent) are the most versatile of these. Coordination and cold-Freon problems are largely eliminated, because the dose may be fired into the spacer and inhaled subsequently (Fig. 2).

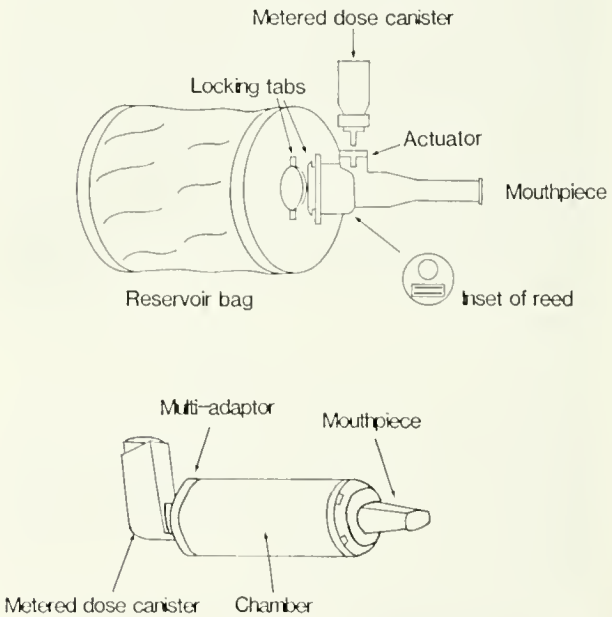


Fig. 2. Two types of spacers, or holding chambers, used with pressurized metered dose inhalers.

Oropharyngeal deposition from spacer devices is always less than that from a standard MDI, and this may reduce both the local[64] and systemic effects[76,77] of topical corticosteroids (Table 4). Lung deposition may be greater than that from a correctly used MDI, but the fractionation of the dose among lungs, oropharynx, and spacer walls varies according to spacer design.[78-80] After reviewing more than 30 clinical studies, Konig[81] concluded that spacers invariably maintain and often enhance the clinical effects of MDI bronchodilators, presumably because

they can 'correct' for poor MDI technique in an important proportion of patients. There is, however, no clear evidence that they confer greater bronchodilator efficacy than a correctly used pressurized MDI (Table 4). In addition to their use in asthma, topical corticosteroids have been used successfully in patients with pulmonary sarcoidosis, either through Brethancer tube spacer[82] or Nebuhaler.[83]

Spacers retain most of the practical advantages of the standard MDI, but are obviously more bulky and less convenient. However, they may be especially useful in a domiciliary situation,[84,85] with patients using them morning and evening at home but using a conventional MDI when they are away from home during the day. Some models can, when equipped with a face mask, be used to deliver pressurized bronchodilator or corticosteroid aerosols to children as young as 1 year of age.[86-88] The flowrates needed to open the inhalation valves on Nebuhaler and Volumatic are very low and are within the capabilities of infants, although the flows at which the valves close are higher.[89]

Table 4. Drug Delivery from Spacer Devices

Lung Deposition
Comparable to or greater than from correctly used MDI
Oropharyngeal Deposition
Always less than from MDI
Clinical Consequences
Bronchodilator efficacy similar to correctly used MDI
Bronchodilator efficacy greater than incorrectly used MDI
Reduction in local and systemic side effects of topical corticosteroids
Possibility of asthma control with smaller drug dose than from MDI?
Unknowns
Few comparisons of different spacers
Optimal inhalation techniques poorly understood
Permissible MDI-spacer combinations?
Few studies on inhaled corticosteroids

Spacers vs Nebulisers

Various spacers (including Nebuhaler,[90,91] Aerochamber,[92] and InspirEase[93]) have been used successfully as alternatives to nebulisers for delivery of large doses of bronchodilators in patients with acute severe asthma and chronic severe asthma. Generally, bronchodilators are effective in smaller doses when given to these patients by spacer than when given by nebuliser.[94] Compared to nebulisers, spacers are cheaper, more portable, and easier to clean.

It is often assumed that patients with severe airways obstruction will be unable to use a conventional pressurized MDI unless it is coupled to a spacer, yet Jenkins et al[95] and Mestitz et al[96] have demonstrated the equivalence of equipotent doses of bronchodilator from MDI and from nebuliser in patients with severe chronic airflow limitation and yet good inhaler technique. In the former of these two studies, patients attributed their well-being to nebulisers, without any objective evidence. This demonstrates an important general point—namely, that successful therapy depends upon the dose of drug delivered to the lung, regardless of how it is achieved.

A small valved spacer device (AeroVent) was more efficient than a Bennett Twin-Jet nebuliser when placed in a ventilator circuit.[51] A mean 5.6% of the dose from the AeroVent was deposited in the lungs of the 9 patients receiving mechanical ventilation, either via endotracheal tube or by tracheostomy, compared to only 1.2% in 11 patients treated by nebuliser. However, in an in-vitro model, a larger spacer (Nebuhaler) was less efficient than a Cirrus nebuliser,[97] perhaps reflecting the variations in performance between different spacers and between different nebulisers.

Unknowns about Spacers

Some important clinical questions about spacers and chambers remain largely unanswered. The deposition efficiency and subsequent drug efficacy from these devices probably depends on the mode of inhalation adopted,[98,99] but this has not been investigated at all for most models. Tidal breathing of single doses is a satisfactory mode of inhalation for the Nebuhaler,[100] and 200 μg of albuterol inhaled from an Aerochamber by four tidal breaths was as effective as 2.5 mg of nebulized albuterol.[92] Nebuhaler retains an efficacy even with delay times as long as 30 seconds between firing the dose and commencing inhalation.[99] It would, however, be wrong to extrapolate these findings automatically to other models; more studies that explore precisely how to use various spacers are required.

For convenience, the inhalation of multiple doses in a single breath from spacers has been advocated, although drug delivery to the lungs will be less than that from the same number of single doses inhaled as one dose per breath.[78] Clark et al[101] found that firing two doses of cromolyn sodium, followed immediately by two doses of albuterol, into InspirEase and Aerochamber resulted in the loss of about two thirds of the cromolyn sodium available from the mouthpiece, compared to that available from two doses of cromolyn sodium alone. On the basis of their study, multiple dosing from spacer devices cannot be recommended.

Some spacers are fitted with adapters that can physically accommodate any brand of MDI, while others can take only specific actuators and canisters. From the point of view of spray kinetics, the extent to which any MDI can be coupled to any spacer is unknown; some MDI-spacer combinations might result in unacceptably low drug delivery because of high droplet impaction on chamber walls. There is also a shortage of data on deposition from spacers equipped with face masks.

More comparative clinical studies of different spacers are required; studies of inhaled corticosteroids delivered from spacer devices have also been inadequate.

Dry Powder Inhalers

Powder Inhalers vs Pressurized MDIs

Powder inhalers share many of the practical advantages of pressurized MDIs, being quick to use, small, and portable. They do not use CFCs, and because they are breath-actuated they are easier to use than pressurized devices. Powder inhalers are more effective than MDIs in patients with poor MDI technique.[102]

Single-dose models such as Rotahaler (for albuterol and beclomethasone dipropionate) and Spinhaler (for cromolyn sodium) contain the drug in gelatine capsules, which must be loaded individually into the device before use (Fig. 3).[103] This serious practical disadvantage has been overcome to varying degrees in two new multidose powder inhalers, the 8-dose Diskhaler (for albuterol and for beclomethasone dipropionate) and the 200-dose Turbuhaler (for terbutaline sulphate and for budesonide). For day-to-day maintenance therapy of asthma, multidose powder inhalers have proved efficacious, easy to use, and popular amongst patients when compared with both pressurized MDI[104-106] and single-dose powder devices.[107] They could thus play a major role in future asthma therapy, if we bear in mind the difficulties that many patients experience in using pressurized MDIs, and the uncertain future of MDIs in the light of the proscription of CFCs.

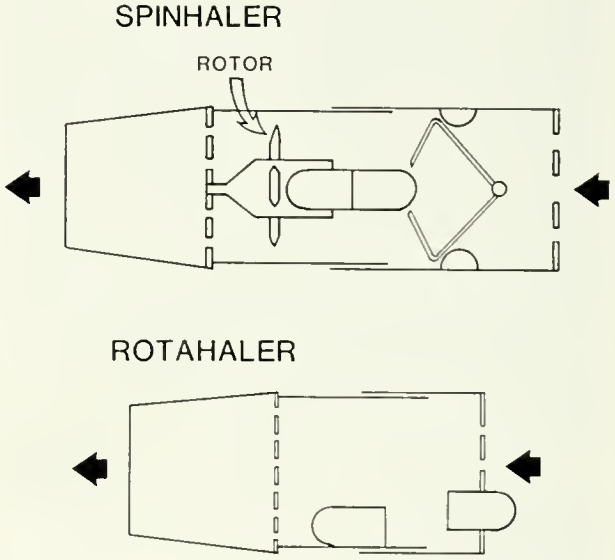


Fig. 3. Two commercially available single-dose dry-powder inhalers. (Reprinted, with permission, from Reference 103.)

In order to fill the inhaler and to overcome cohesive forces between drug particles and the walls of the device, there are currently two formulations of powder inhaler. Micronized drug powder is either spheronized into visible agglomerates or is mixed with a coarse lactose carrier. From the patient's point of view, the presence of a carrier has both advantages and disadvantages. The deposition of large amounts of carrier on the back of the throat may cause irritation, although the patient may at the same time feel reassured that a dose has been delivered. It should be borne in mind, however, that simply feeling a dose on the back of the throat is no guarantee that any of it has been inhaled.

Some drug substances delivered by powder inhaler are water soluble, and humidity may affect the performance of powder inhalers to a greater extent than it affects the performance of MDIs.

Information is lacking on the efficacy of powder inhalers in severe and life-threatening episodes of asthma, and existing models probably cannot be effectively incorporated into ventilator circuits.

Deposition Efficiency and Inhalation Modes

The deposition efficiency of both single-dose[108] and multidose powder inhalers[109,110] is comparable to that of a pressurized MDI, although the fractionation of the dose between amounts delivered to the lungs and oropharynx and the amount retained in the device varies according to type of inhaler. As with the pressurized MDI, the majority of the dose is deposited in the oropharynx because it is contained in particles $\geq 5\ \mu m$ in diameter—too large for inhalation. Powder inhalers and pressurized MDIs have a similar efficacy, although for Rotahaler the standard doses of bronchodilator and corticosteroid are twice those of the MDI, and in the Spinhaler a rather high dose of cromolyn sodium (20 mg) is used, apparently in order to extend the duration of drug action.

The efficiency of powder inhalers is optimised by rapid inhalation,[111,112] which causes the drug particles or drug-lactose agglomerates to de-aggregate in a turbulent airstream, thus ensuring an adequate yield of respirable particles. All currently available devices (1990) behave in this manner, and for each device a minimum inspiratory flowrate must be maintained for full drug efficacy. For Turbuhaler, this 'critical' flowrate appears to be approximately 30 L/min; this flow can be attained by virtually any adult asthmatic[113] and virtually all children > 6 years of age, although many young children (< 6 years of age) with acute wheezing may be less successful in reaching this flowrate.[112] The addition of head-tilting, breath-holding, and preliminary exhalation to residual volume does not augment the therapeutic effect of rapid inhalation from Turbuhaler in children;[114] hence, a simple inhalation technique is possible, which encourages compliance.

Concluding Remarks

In order to be effective, aerosol inhalers must deliver an adequate quantity of drug to the lower respiratory tract. All devices deliver a broadly similar small percentage of the dose to the lungs, and with correct

Table 5. Practical Features of Aerosol Delivery Devices

Feature	Nebuliser	MDI alone	Spacer	Powder Inhaler
Quick to use?	No	Yes	Yes	Yes
Cheap?	No	Yes	Yes	Yes*
Compact?	No	Yes	No	Yes
Electricity-free?	No	Yes	Yes	Yes
Portable?	No	Yes	(Yes)†	Yes
Multidose?	No	Yes	Yes	Some models
Hard to contaminate?	No	Yes	Yes	Yes
Additive-free?	Maybe	No	No	Maybe
CFC-free?	Yes	No	No	Yes
Easy inhalation technique?	Yes	No	(Yes)	(Yes)
Suitable for very young?	Yes	No	Yes	No
Large doses convenient?	Yes	No	Yes	No
'OK' in acute severe asthma?	Yes	??	Yes	??
'OK' in ventilator circuits?	Yes	??	Yes	No
Unusual drugs possible?	Yes	No	No	No
Low mouth deposition?	Yes	No	Yes	No

*But costs more than MDI.
†(Yes) indicates limitations.

use this percentage is on average greater for pressurized MDIs and for powder devices than for nebulisers. At least for inhaled bronchodilators, it does not seem critical to deliver the drug directly to peripheral airways, perhaps because some redistribution within the lungs occurs in local circulation.[115] Specialized nebulisers giving a very low but highly selective deposition in the alveoli may be appropriate for targeting the lung parenchyma. Drug delivery from MDIs and spacers probably depends more upon the mode of inhalation than upon the type of apparatus used, while for nebulisers the reverse is the case. There is wide intersubject variability in deposition, which makes it impossible to predict the lung dose that any individual will receive.

Table 5 lists some desirable practical features of inhalation devices, showing whether various types of inhalation devices possess these features. A number of general conclusions can be drawn from the table: (1) pressurized MDIs and powder inhalers have a range of positive features that are mostly different from those possessed by nebulisers; MDIs and powder inhalers on the one-hand, and nebulisers on the other, thus represent opposite ends of the spectrum of inhalation therapy. MDIs (providing they are equipped with 'ozone-friendly' propellants) and powder inhalers are likely to remain the devices of choice for day-to-day maintenance therapy of asthma, and multidose powder inhalers may be used increasingly. There is a definite role for breath-actuated pressurized devices. Nebulisers fulfill other roles (for instance, the treatment of severe disease, therapy in circumstances in which other devices are inappropriate, and delivery of unusual drug substances). (2) Spacer devices coupled to an MDI have many of the positive features of the standard MDI, but also fulfill some of the roles of nebulisers, including delivery of bronchodilators in severe acute asthma and incorporation into ventilator circuits; these versatile devices may be underrated. (3) Perhaps the most important conclusion is that there is no such thing as a perfect inhalation device, and we need to utilize a full range of inhalation technology if aerosol therapy is to fulfill its huge potential.

PRODUCT SOURCES

Aerochamber, Monaghan Medical Corp, Plattsburgh NY
AeroVent, Monaghan Medical Corp, Plattsburgh NY
Autohaler, 3M Health Care, St Paul MN
Twin-Jet nebuliser, Puritan-Bennett Corp, Lenexa KS
Brethancer, Ciba-Geigy Corp, Summit NJ
Cadema nebuliser, Cadema Medical Products Inc, Middletown NY
Cirrus nebuliser, Intersurgical Ltd, Twickenham, England
CR 60 compressor, Medic-Aid Ltd, Chichester, England
DeVilbiss 646 nebuliser, DeVilbiss International, Somerset PA
Diskhaler, Glaxo/Allen and Hanburys, Research Triangle Park NC
GentleHaler, Schering-Plough Corp, Kenilworth NJ
InspirEase, Schering-Plough Corp, Kenilworth NJ
Maxi III compressor, Medix, Lutterworth, England
Mizer storage device, Medic-Aid Ltd, Chichester, England
Nebuhaler, Astra Pharmaceuticals, Lund, Sweden
Respirgard II nebuliser, Marquest Medical Products, Englewood CO
Rondo, Leiras Pharmaceuticals, Turku, Finland
Rotahaler, Glaxo/Allen and Hanburys, Research Triangle Park NC
SPAG-2 Collison nebuliser, Viratek Inc, Costa Mesa CA
Spinhaler, Fisons Pharmaceuticals, Rochester NY
Turbuhaler, Astra Pharmaceuticals, Lund, Sweden
Turret nebuliser, Medic-Aid Ltd, Chichester, England
Ultravent nebuliser, Mallinckrodt, St Louis MO
Volumatic, Glaxo/Allen and Hanburys, Research Triangle Park NC

REFERENCES

1. Graeser JB, Rowe AH. Inhalation of epinephrine for relief of asthmatic symptoms. J Allergy 1935;6:415-420.
2. Mercer TT. Production of therapeutic aerosols: principles and techniques. Chest 1981;80(6, Suppl):813-818.
3. Newman SP. Nebuliser therapy: scientific and technical aspects. Lund, Sweden: AB Draco, 1989.
4. Kohler D, Matthys H. Correspondence (letter). J Aerosol Sci 1984;15:519.
5. Matthys H, Kohler D. Pulmonary deposition of aerosols by different mechanical devices. Respiration 1985;48: 269-276.
6. Lewis RA, Ellis CJ, Fleming JS, Balachandran W. Ultrasonic and jet nebulizers: differences in the physical properties and fractional deposition on the airway responses to nebulized water and saline aerosols (abstract). Thorax 1984;39:712.
7. Swift DL. Aerosol characterization and generation. In: Morén F, Newhouse MT, Dolovich MB, eds. Aerosols in medicine: principles, diagnosis and therapy. Amsterdam: Elsevier, 1985:53-76.
8. Wood JA, Wilson RSE, Bray C. Changes in salbutamol concentration in the reservoir solution of a jet nebuliser. Br J Dis Chest 1986;80:164-169.
9. Stainforth JN, Lewis RA, Tattersfield AE. Dosage and delivery of nebulized beta-agonists in hospital. Thorax 1983;38:751-754.
10. Murphy D, Holgate ST. The use and misuse of domiciliary nebulizer therapy in the Isle of Wight. Respir Med 1989;83:349-352.

11. Steventon RD, Wilson RSE. A guide to apparatus for home nebuliser therapy. Research Triangle Park NC: Allen and Hanburys, 1986.
12. Sterk PJ, Plomp A, Van der Vate JF, Quanjer PH. Physical properties of aerosols produced by several jet and ultrasonic nebulisers. Bull Eur Physiopathol Respir 1984;20:65-72.
13. Newman SP, Pellow PGD, Clay MM, Clarke SW. Evaluation of jet nebulisers for use with gentamicin solution. Thorax 1985;40:671-676.
14. Smith EC, Kendrick AH. Comparison of apparatus for home nebuliser therapy (abstract). Thorax 1990;45:817.
15. Juniper EF, Hargreave FE. Airway responsiveness assessed by aerosol inhalation tests: variability in results due to unexpected differences between calibrated nebulizers (abstract). Bull Eur Physiopathol Respir 1986;22(8, Suppl):165S.
16. Tsanakas JN, Wilson AJ, Boon AW. An evaluation of nebulisers for bronchial challenge tests (abstract). Bull Eur Physiopathol Respir 1986;22(8, Suppl):138S.
17. O'Callaghan C, Clark AR, Milner AD. Why nebulize for more than 5 minutes? Arch Dis Child 1989;64:1270-1273.
18. Smye SW, Shaw A, Norwood HM, Littlewood JM. Some factors influencing efficiency of a jet nebuliser system. Clin Phys Physiol Meas 1990;11:167-175.
19. Thomas SHL, Langford JA, George RDG, Geddes DM. Improving the efficiency of drug administration with jet nebulisers (letter). Lancet 1988;1:126.
20. Pisut FM. Comparison of medication delivery by T-nebulizer with inspiratory and expiratory reservoir. Respir Care 1989;34:985-988.
21. Asmundsson T, Johnson RF, Kilburn KH, Goodrich JR. Efficiency of nebulizers for depositing saline in human lung. Am Rev Respir Dis 1973;108:506-512.
22. Lin MS, Hayes TM, Goodwin GA, Kruse SL. Distal penetration in radioaerosol inhalation with an ultrasonic nebuliser. Radiology 1974;112:443-447.
23. Johnson MA, Newman SP, Bloom R, Talaee N, Clarke SW. Delivery of albuterol and ipratropium bromide from two nebulizer systems in chronic stable asthma: efficacy and pulmonary deposition. Chest 1989;96:1-10.
24. Montgomery AB, Debs RJ, Luce JM, Corkery KJ, Turner J, Brunette EN, et al. Aerosolised pentamidine as sole therapy for *Pneumocystis carinii* pneumonia in patients with acquired immunodeficiency syndrome. Lancet 1987;2:480-483.
25. Simonds AK, Newman SP, Johnson MA, Talaee N, Lee CA, Clarke SW. Simple nebuliser modification to enhance alveolar deposition of pentamidine. Lancet 1989;2:953.
26. MacIntyre NR, Silver RM, Miller CW, Schuler F, Coleman RE. Aerosol delivery in intubated, mechanically ventilated patients. Crit Care Med 1985;13:81-84.
27. Ahrens RC, Ries RA, Popendorf W, Wiese JA. The delivery of therapeutic aerosols through endotracheal tubes. Pediatr Pulmonol 1986;2:19-26.
28. Hughes JM, Saez J. Effects of nebulizer mode and position in a mechanical ventilator circuit on dose efficiency. Respir Care 1987;32:1131-1135.
29. Dahlback M, Wollmer P, Drefeldt B, Jonson B. Controlled aerosol delivery during mechanical ventilation. J Aerosol Med 1989;4:339-347.
30. Ryan G, Dolovich MB, Obminski G, Cockcroft DW, Juniper E, Hargreave FE, et al. Standardisation of inhalation provocation tests: influence of nebulizer output, particle size and method of inhalation. J Allergy Clin Immunol 1981;67:156-161.
31. Ruffin RE, Dolovich MB, Wolff RK, Newhouse MT. The effects of preferential deposition of histamine in the human airway. Am Rev Respir Dis 1978;117:485-492.
32. Newman SP, Woodman G, Clarke SW. Deposition of carbenicillin aerosols in cystic fibrosis: effects of nebuliser system and breathing pattern. Thorax 1988;43:318-322.
33. Zainuddin BM, Tolfree SEJ, Short M, Spiro SG. Influence of breathing pattern on lung deposition and bronchodilator response to nebulized salbutamol in patients with stable asthma. Thorax 1988;43:987-991.
34. Salmon B, Wilson NM, Silverman M. How much aerosol reaches the lungs of wheezy infants and toddlers? Arch Dis Child 1990;65:401-403.
35. Dolovich MB, Killian D, Wolff RK, Obminski G, Newhouse MT. Pulmonary aerosol deposition in chronic bronchitis: intermittent positive pressure breathing versus quiet breathing. Am Rev Respir Dis 1977; 115:397-402.
36. IPPB Trial Group. IPPB in COPD. Chest 1984;86:341-342.
37. Thomas SHL, Langford JA, George RJD, Geddes DM. Aerosol deposition in the human lung: effect of high frequency oscillation on the deposition characteristics of an inhaled nebulized aerosol. Clin Sci 1988;75:535-542.
38. O'Doherty M, Thomas S, Page C, Bradbeer C, Nunan T, Bateman N. Is upper lobe deposition of nebulised pentamidine improved by inhalation lying down? (abstract). Montreal, Canada: 5th International AIDS Conference, 1989:300.
39. Collis GG, Cole CH, LeSouef PN. Dilution of nebulised aerosols by air entrainment in children. Lancet 1990;336:341-343.
40. Everard ML, Clark AR, Milner AD. Factors affecting drug delivery from jet nebulisers to patients (abstract). Thorax 1990;45:817.
41. Lewis RA, Fleming JS. Fractional deposition from a jet nebuliser: how it differs from a metered dose inhaler. Br J Dis Chest 1985;79:361-367.
42. Ilowite JS, Gorvoy JD, Smaldone GC. Quantitative deposition of aerosolized gentamicin in cystic fibrosis. Am Rev Respir Dis 1987;136:1445-1449.
43. Hadfield JW, Windebank WJ, Bateman JRM. Is driving gas flow clinically important for nebuliser therapy? Br J Dis Chest 1986;80:50-54.
44. Douglas JG, Leslie MJ, Crompton GK, Grant IWB. A comparative study of two doses of salbutamol nebulized at 4 and 8 L/min in patients with chronic asthma. Br J Dis Chest 1986;80:55-58.
45. Knight V, Gilbert BE. Aerosol treatment of respiratory viral disease. Lung 1990;168(Suppl):406-413.

46. Hubbard RC, Crystal RG. Strategies for aerosol therapy of alpha$_1$-antitrypsin deficiency by the aerosol route. Lung 1990;168(Suppl):565-578.
47. Köhler D. Aerosols for systemic treatment. Lung 1990;168(Suppl):677-684.
48. Chinet T, Collignon M-A, Dusser D, Barritault L, Huchon GJ. Effectiveness of micronic aerosol generators and their aerosol characteristics. Eur J Respir Dis 1986;69:153-159.
49. Ziment I. A prescription for prescription writers (editorial). Respir Care 1986;33:841-843.
50. Mallol J, Barrueto L, Giradi G, Munoz R, Puppo H, Ulloa V, et al. Use of nebulized bronchodilators in infants under one year of age. Pediatr Pulmonol 1987;3:298-303.
51. Fuller HD, Dolovich MB, Posmituck G, Wong Pack W, Newhouse MT. Pressurized aerosol versus jet aerosol delivery to mechanically ventilated patients: comparison of dose to the lungs. Am Rev Respir Dis 1990;141:440-444.
52. Hodson ME, Penketh ARL, Batten JC. Aerosol carbenicillin and gentamicin treatment of pseudomonas infection in patients with cystic fibrosis. Lancet 1981;2:1137-1139.
53. Rafferty P, Beasley R, Holgate ST. Comparison of the efficacy of preservative-free ipratropium bromide and Atrovent nebuliser solutions. Thorax 1988;43:446–450.
54. Snell NJC. Adverse reactions to inhaled drugs. Respir Med 1990;84:345-348.
55. Anonymous. The nebuliser epidemic (editorial). Lancet 1984;2:789-790.
56. Cochrane GM, Prior JG, Rees PJ. Home nebulisers for airflow limitation (editorial). Br Med J 1985;290:1608-1609.
57. Morén F. Aerosol dosage forms and formulations. In: Morén F, Newhouse MT, Dolovich MB, eds. Aerosols in medicine: principles, diagnosis and therapy. Amsterdam: Elsevier. 1985:261-287.
58. Hallworth GW. The formulation and evaluation of pressurized metered dose inhalers. In: Ganderton D, Jones T, eds. Drug delivery to the respiratory tract. Chichester, England: Ellis Horwood, 1987:87-118.
59. Newman SP, Pavia D, Morén F, Sheahan NF, Clarke SW. Deposition of pressurized aerosols in the human respiratory tract. Thorax 1981;36:52-55.
60. Dolovich MB, Ruffin RE, Roberts R, Newhouse MT. Optimal delivery of aerosols from metered dose inhalers. Chest 1981;83(Suppl):911-915.
61. Spiro SG, Singh CA, Tolfree SEJ, Partridge MR, Short MC. Direct labelling of ipratropium bromide aerosol and its deposition pattern in normal subjects and patients with chronic bronchitis. Thorax 1984;39:432–435.
62. Vidgren MT, Karkkainen A, Karjalainen P, Paronen P. A novel labelling method for measuring the deposition of drug particles in the respiratory tract. Int J Pharm 1987;37:239-244.
63. Kohler D, Fleischer W, Matthys H. A new method for easy labelling of beta$_2$-agonists in the metered dose inhaler with Tc99m. Respiration 1988;53:65-73.
64. Toogood JH, Baskerville J, Jennings B, Lefcoe NM, Johansson S-A. Use of spacers to facilitate inhaled corticosteroid treatment in asthma. Am Rev Respir Dis 1984;129:723-729.
65. Newman SP, Pavia D, Clarke SW. How should a pressurized beta-adrenergic bronchodilator be inhaled? Eur J Respir Dis 1981;62:3-20.
66. Ruffin RE, Montgomery JM, Newhouse MT. Site of beta-adrenergic receptors in the respiratory tract. Chest 1978;74:256-260.
67. Lindgren S, Bake B, Larsson S. Clinical consequences of inadequate inhalation technique in asthma therapy. Eur J Respir Dis 1987;70:93-98.
68. Crompton GK, Duncan J. Clinical assessment of a new breath-actuated inhaler. Practitioner 1989;233:268-269.
69. Woodcock A. Training aid for pressurized inhalers. Br J Dis Chest 1980;74:395-397.
70. Shim C, Williams MH. The adequacy of inhalation of aerosol from canister nebulisers. Am J Med 1980;65:891-894.
71. Altounyan REC, Cole M, Clark AR. Evaluation of an "open" spacer device for sodium cromoglycate (abstract). Eur J Respir Dis 1983;64(Suppl 126):540.
72. Newman SP, Weisz A, Clarke SW. Bronchodilator delivery from GentleHaler, a new low-velocity pressurized aerosol inhaler (abstract). Am Rev Respir Dis 1990;141(4, Part 2):A18.
73. Crompton GK. The adult patient difficulties with inhalers. Lung 1990;168(Suppl):658-662.
74. Newman SP. Metered dose pressurized aerosols and the ozone layer. Eur Respir J 1990;3:495–497.
75. Yarbrough J, Mansfield LE, Ting S. Metered dose inhaler-induced bronchospasm in asthmatic patients. Ann Allergy 1985;55:25-27.
76. Brown PH, Blundell G, Greening AP, Crompton GK. Do large volume spacers reduce the systemic effects of high dose inhaled corticosteroids? Thorax 1990;45:736-739.
77. Farrer M, Francis AJ, Pearce SJ. Morning serum cortisol concentrations after 2 mg inhaled beclomethasone dipropionate in normal subjects: effect of a 750 mL spacing device. Thorax 1990;45:740-742.
78. Newman SP, Millar AB, Lennard-Jones TR, Morén F, Clarke SW. Improvement of pressurized aerosol deposition with Nebuhaler spacer device. Thorax 1984;39:935-941.
79. Dolovich MB, Ruffin R, Corr D, Newhouse MT. Clinical evaluation of a new demand-inhalation MDI aerosol delivery device. Chest 1983;84:36–41.
80. Vidgren MT, Paronen P, Karkkainen A, Karjalainen P. Effect of extension devices on drug deposition from inhalation aerosols. Int J Pharm 1987;39:107-112.
81. Konig P. Spacer devices used with metered dose inhalers: breakthrough or gimmick? Chest 1985;88:276-284.
82. Selroos O. Use and limits of topical aerosols for topical treatment of granulomas and airflow obstruction in sarcoidosis. Sarcoidosis 1986;3:126-127.
83. Spiteri MA, Newman SP, Clarke SW, Poulter LW. Inhaled corticosteroids can modulate the immunopathogenesis of pulmonary sarcoidosis. Eur Respir J 1989;2:218-224.

84. Russel G, Frame M. Terbutaline by Nebuhaler in young children. Practitioner 1986;230:1043-1046.
85. O'Reilly JF, Gould G, Kendrick AH, Laszlo G. Domiciliary comparison of terbutaline treatment by metered dose inhaler with and without conical spacer in severe and moderately severe chronic asthma. Thorax 1986;41:766-770.
86. Bisgaard H, Munck SL, Nielsen JP, Petersen W, Ohlsson SV. Inhaled budesonide for treatment of recurrent wheezing in early childhood. Lancet 1990;336:649-651.
87. McCarthy TP. Nebulized budesonide in severe childhood asthma (letter). Lancet 1989;1:379-380.
88. Mallol J, Barrueto L, Girardi G, Toro O. Bronchodilator effect of fenoterol and ipratropium bromide in infants with acute wheezing: use of MDI with a spacer device. Pediatr Pulmonol 1987;3:352-356.
89. Sennhauser FH, Sly PD. Pressure-flow characteristics of the valve in spacer devices. Arch Dis Child 1989;64:1305-1309.
90. Morgan MDL, Singh BV, Frame MF, Williams SJ. Terbutaline aerosol given through pear shaped spacer in acute severe asthma. Br Med J 1982;285:849-850.
91. Fuglsang G, Pedersen S. Comparison of Nebuhaler and nebulizer treatment of acute severe asthma in children. Eur J Respir Dis 1986;69:109-113.
92. Gervais A, Bégin P. Bronchodilatation with a metered-dose inhaler plus an extension, using tidal breathing vs jet nebulization. Chest 1987;92:822-824.
93. Turner JR, Corkery KJ, Eckman D, Gelb AM, Lipavsky A, Sheppard D. Equivalence of continuous flow nebulizer and metered dose inhaler with reservoir bag for treatment of acute airflow obstruction. Chest 1988;93:476-481.
94. Noseda A, Yernault JC. Sympathomimetics in acute severe asthma: inhaled or parenteral, nebulizers or spacer. Eur Respir J 1989;2:377-382.
95. Jenkins SC, Heaton RW, Fulton TJ, Moxham J. Comparison of domiciliary nebulized salbutamol and salbutamol from a metered dose inhaler in stable chronic airflow limitation. Chest 1987;91:804-807.
96. Mestitz H, Copland JM, McDonald CF. Comparison of outpatient nebulized vs metered dose inhaler terbutaline in chronic airflow obstruction. Chest 1989;96:1237-1240.
97. Simonds AK, Newman SP, Cox D, Clarke SW. Aerosol delivery during mechanical ventilation: nebuliser or Nebuhaler? (abstract). Thorax 1990;45:315P.
98. Pedersen S. Optimal use of tube spacer aerosols in asthmatic children. Clin Allergy 1985;15:473-478.
99. Newman SP, Woodman G, Morén F, Clarke SW. Bronchodilator therapy with Nebuhaler: how important is the delay between firing and inhaling? Br J Dis Chest 1987;82:262-267.
100. Gleeson JGA, Price JF. Nebuhaler technique. Br J Dis Chest 1988;82:172-174.
101. Clark AR, Rachelevsky G, Mason PL, Goldenhersh MJ, Hollingworth A. The use of reservoir devices for the simultaneous delivery of two metered dose aerosols. J Allergy Clin Immunol 1990;85:75-79.
102. Crompton GK. Clinical use of dry powder systems. Eur J Respir Dis 1982;122(Suppl):96-99.
103. Newman SP. Production of radioaerosols. In: Clarke SW, Pavia D, eds. Aerosols and the lung. London: Butterworths, 1984:71-91.
104. Persson G, Gruvstad E, Stahl E. A new multiple dose powder inhaler (Turbuhaler) compared with a pressurized inhaler in a study of terbutaline in asthmatics. Eur Respir J 1988;1:681-684.
105. Engel T, Heinig JH, Malling H-J, Scharling B, Nikander K, Madsen F. Clinical comparison of inhaled budesonide delivered either via pressurized metered dose inhaler or Turbuhaler. Allergy 1989;44:220-225.
106. Drepaul BA, Payler DK, Qualtrough JE, Perry LJ, Reeve FBA, Charlton SC. Becotide or Becodisks? A controlled study in general practice. Clin Trials J 1989;26:335-344.
107. Anani A, Higgins AJ, Crompton GK. Breath-actuated inhalers: comparison of terbutaline Turbuhaler with salbutamol Rotahaler. Eur Respir J 1989;2:640-642.
108. Vidgren MT, Karkkainen A, Karjalainen P, Paronen P, Nuutinen J. Effect of powder inhaler design on drug deposition in the respiratory tract. Int J Pharm 1988;42:211-216.
109. Newman SP, Morén F, Trofast E, Talaee N, Clarke SW. Deposition and clinical efficacy of terbutaline sulphate from Turbuhaler, a new multi-dose powder inhaler. Eur Respir J 1989;2:247-252.
110. Vidgren MT, Paronen P, Vidgren P, Vainio P, Nuutinen J. In-vivo evaluation of the new multiple dose powder inhaler and Rotahaler using gamma scintigraphy. Acta Pharm Nord 1990;1:3-10.
111. Pedersen S. How to use a Rotahaler. Arch Dis Child 1986;61:11-14.
112. Pedersen S, Hansen OR, Fuglsang G. Influence of inspiratory flowrate upon the effect of a Turbuhaler. Arch Dis Child 1990;65:308-310.
113. Engel T, Heinig JH, Madsen F, Nikander K. Peak inspiratory flowrate and inspiratory vital capacity of patients with asthma measured with and without a new dry powder inhaler device (Turbuhaler). Eur Respir J 1990;3:1037-1041.
114. Hansen OR, Pedersen S. Optimal inhalation technique with terbutaline Turbuhaler. Eur Respir J 1989;2:637-639.
115. Ryrfeldt A. The bronchial circulation—a significant local distribution system in the lung in inhalation therapy? J Aerosol Med 1990;3:165-168.

The Interface between Patient and Aerosol Generator

Robert M Kacmarek PhD RRT and Dean Hess MEd RRT

Introduction

Historically, aerosol therapy has been delivered primarily by small volume nebulizer (SVN) (Fig. 1). However, recent data imply that the metered dose inhaler (MDI) (Fig. 2) is at least equivalent to SVN in most clinical settings and is being used more frequently in both spontaneously breathing and mechanically ventilated patients. In addition, the use of the dry powder inhaler (DPI) (Fig. 3) is increasing in the United States and has become commonplace in many European countries for administration of aerosols to spontaneously breathing patients.

Fig. 1. Small volume nebulizer.

Fig. 2. Metered dose inhaler.

We review and compare the efficacy of various methods of aerosol delivery, and discuss and describe protocols for the interface of patients with these delivery systems.

Fig. 3. Single-dose dry powder inhalers: Rotahaler (right) and Spinhaler (left).

Dr Kacmarek is Assistant Professor, Department of Anesthesiology, Harvard Medical School, and Director, Respiratory Care, Massachusetts General Hospital– Boston, Massachusetts. Mr Hess is Assistant Director of Research, York Hospital, and Instructor, School of Respiratory Therapy, York Hospital and York College of Pennsylvania, York, Pennsylvania.

A version of this paper was presented by Dr Kacmarek at the Consensus Conference on Aerosol Delivery, sponsored by the American Association for Respiratory Care, the American Respiratory Care Foundation, and the journal RESPIRATORY CARE, January 10-12, 1991, in Cancun, Mexico.

Reprints: Robert M Kacmarek PhD RRT, Respiratory Care, Ellison 4, Massachusetts General Hospital, Boston MA 02114.

Aerosol Therapy during Spontaneous Breathing

Small Volume Nebulizers

Factors Affecting Efficacy

The efficacy of SVN in spontaneously breathing patients is influenced by many factors: solution volume,[1-3] nebulizer flowrate,[2,4,5] intermittent vs continuous nebulization,[6,7] nebulizer design,[2,8,9] and temperature and humidity of driving and entrained gas.[10,11] However, even under optimal conditions, only about 8-12% (Fig. 4) of the drug is deposited in the lower respiratory tract.[12,13]

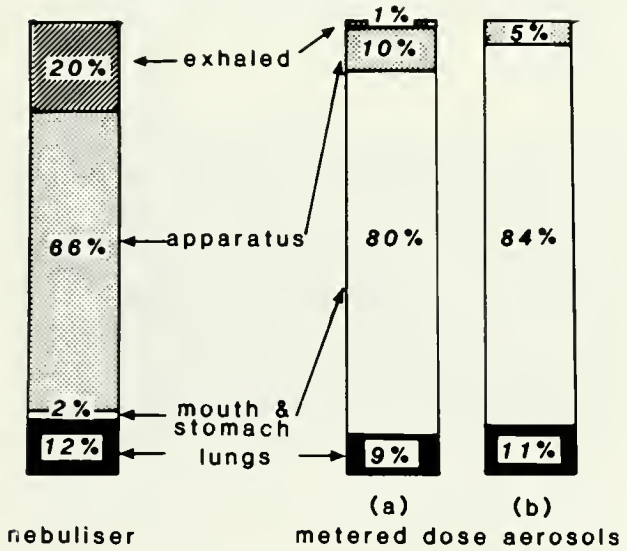


Fig. 4. Fractional deposition of aerosol from jet nebulizer (left), compared to fractional deposition from an MDI (two columns on right). (a) ^{99}Tc-labeled Teflon particles from Newman et al[34] and (b) ^{77}Br-labeled ipratropium bromide from Spiro et al.[35] (Reprinted, with permission, from Reference 13.)

Dead Volume. Regardless of nebulizer design, some of the solution (dead volume) remains in the nebulizer after completion of a treatment. Depending on the design of the SVN selected, the dead volume varies from about 0.5 to 1.0 mL,[14,15] and represents the solution adhering to the walls, cap, and system connections to the patient (ie, corrugated tubing, mouthpiece, and mask). Tapping the sides of the nebulizer during therapy causes droplets of solution adhering to the walls of the nebulizer to coalesce and be renebulized, and thus maintains dead volume at a minimum. To ensure minimum dead volume and maximum aerosolization of the solution, nebulization with repetitive tapping of the nebulizer should continue until no aerosol is produced by the nebulizer or the nebulizer is 'dry.'

The quantity of the medication remaining in solution in the dead volume is dependent on the total volume of solution;[1-3] the nebulizer flowrate;[2,4,5] and the temperature and humidity of the solution, driving gas, and entrained gas.[10,11] Hess et al,[2] in a bench study, demonstrated that the volume of drug aerosolized increased with increasing diluent volume and nebulizer flowrate (Fig. 5). The maximum volume of drug delivery occurred at a total solution volume of about 4 mL and a nebulizer flow of 6-8 L/min. Similar results were reported by Clay et al,[1] Wood et al,[3] Clay et al,[4] and Douglas et al.[5] Clay et al[4] also demonstrated that the mass median aerodynamic diameter (MMAD) of aerosol particles from four nebulizers (Fig. 6) decreased as flowrate increased from 4 to 8 L/min. However, Hadfield et al,[16] in 10 stable asthmatic patients, noted no difference in physiologic response between a total solution volume of 2 and 4 mL nebulized at flowrates of 4, 6, and 8 L/min. Kradjan and Lakshminarayan[6] found a solution volume of 2.0-2.5 mL optimal, although they only examined volumes up to 3.0 mL. In spite of this controversy, we believe sufficient data exist to recommend the use of a total solution volume of 4 mL at a nebulizer flowrate of 6-8 L/min.

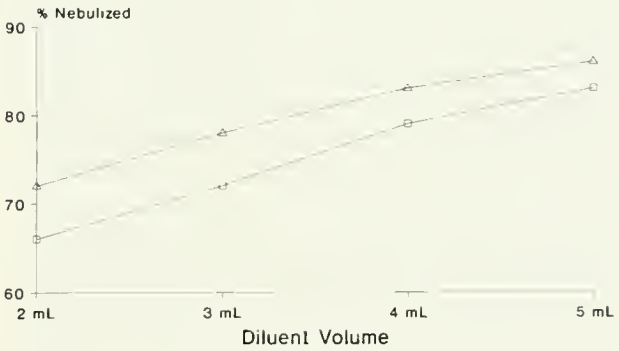


Fig. 5. Effects of flow and diluent volume on nebulizer dead volume. □ = 6 L/min flow; Δ = 8 L/min. (Reprinted, with permission, from Reference 2.).

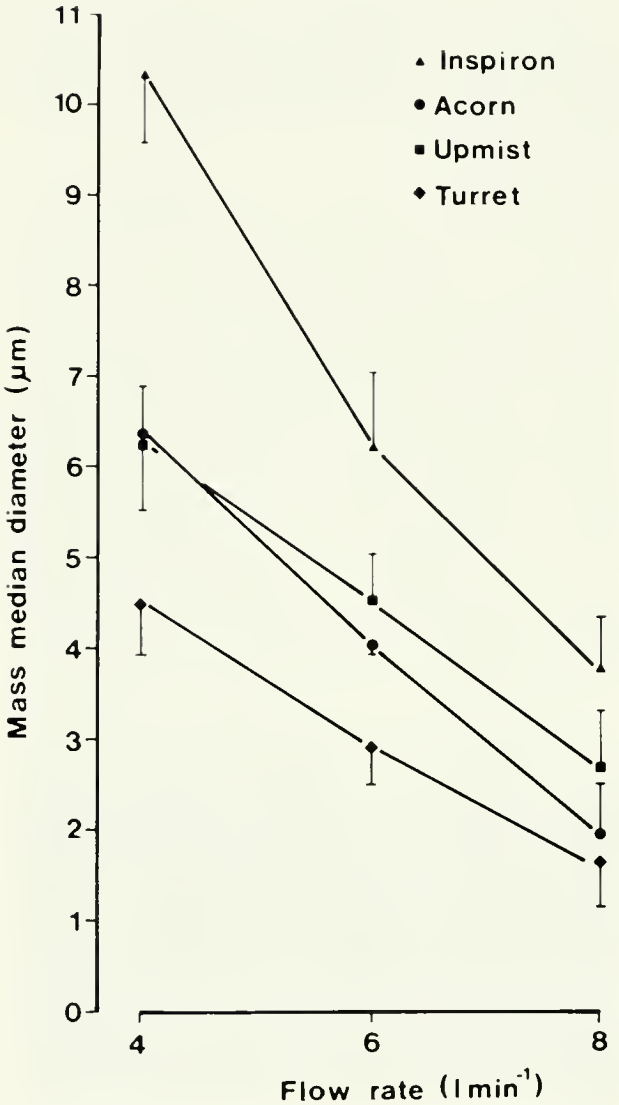


Fig. 6. Effect of varying the flowrate of compressed air used to drive nebulizers on the mass median aerodynamic diameter of aerosol generated. The points shown represent pooled data for concentration and nebulization times and are the means and standard errors of five nebulizers of each type listed on figure. (Adapted, with permission, from Reference 4.)

Temperature and Humidity. Temperature and humidity of the nebulized solution and of driving and entrained gas affect the size of particles delivered by SVNs and the concentration of the drug in the dead volume.[9,10] Evaporation of water and adiabatic expansion of the driving gas[17,18] reduce the temperature of aerosol solutions to about 8-12°F below that of the environment.[9] The evaporation of water also increases the concentration of the drug in the solution in the nebulizer. Because gas temperature increases as the aerosol is warmed to room temperature, particle size of the aerosol is reduced. Therefore, although impractical clinically, nebulizer solutions should be maintained at a temperature between that of the ambient environment and body temperature, and the gas entrained should be saturated with water vapor at room temperature to stabilize particle size. From a practical perspective, a mechanical compressor (compressing room air) is preferable to cylinder gas because of water vapor content. Temperature change in the solution can be minimized by holding the SVN firmly in the closed hand.

Technique and Ventilatory Pattern. Aerosol from SVNs should be inhaled via the mouth, rather than the nose, to minimize deposition of the drug in the nose and nasopharynx[19] (Table 1). Upper-airway deposition is increased with nasal breathing because of the tortuous route the aerosol must follow and the high resistance to gas flow.[20] However, when patients with face masks inspire through the mouth, no difference in response between mask and mouthpiece aerosol delivery has been demonstrated.[21,22] In fact, many patients prefer delivery

Table 1. Technique for Use of a Small Volume Nebulizer (SVN)

Place drug in nebulizer.
Dilute with physiologic saline (0.9%) to 4 mL total volume.
Incorporate a finger port into the driving gas system to provide intermittent nebulization during inspiration only.
Set driving gas flow at 6-8 L/min.
Connect patient to SVN via a mouthpiece or mask (in some patients a nose clip may be necessary).
Instruct patient to inspire through open mouth if using a mask or to close lips around mouthpiece.
Grasp nebulizer chamber firmly in hand to maintain temperature during treatment.
Have patient inhale slowly (0.5 L/s) at normal tidal volume.
Have patient occasionally inspire to total lung capacity and incorporate a 4-10 second breath-hold.
Tap sides of nebulizer to minimize dead volume.
Continue treatment until no aerosol is produced.
Monitor patient for presence of side effects (eg, tachycardia or tremor) and beneficial effects (eg, improved breath sounds, peak flow, and FEV_1).

via face mask, and the use of a face mask may improve compliance.

Intermittent activation of SVN versus continuous administration has also been evaluated.[6,23] Both Kradjan and Lakshminarayan[6] and Hughes et al[23] found greater amounts of drug delivered to lung models with intermittent (inspiration only) activation of the SVN because all of the solution nebulized during expiration is lost to the environment (Fig. 7). However, intermittent nebulization greatly prolongs the treatment and affects compliance in the less-than-enthusiastic patient. As a result, even though intermittent nebulization is preferable for optimal deposition, continuous aerosolization may be necessary from a practical perspective to ensure compliance. The actual protocol used must be individualized.

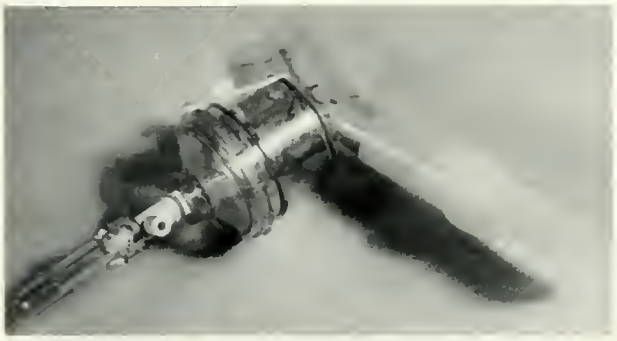


Fig. 7. Small volume nebulizer with finger port adapter to allow for intermittent nebulization. Flow to nebulizer controlled by patient occlusion of finger port.

Ventilatory pattern does influence deposition of nebulized aerosols in the lower respiratory tract.[24-26] Although some controversy exists over the ideal ventilatory pattern, a slow inspiratory flow (0.5 L/min)[24,25] at tidal volume, with an occasional inspiration to total lung capacity (TLC) and an inspiratory hold, is recommended.[26]

Metered Dose Inhalers without Spacing Devices

MDIs are available for the administration of bronchodilators, anticholinergics, and steroids, and have compared favorably with SVNs in a number of recent studies.[27-33] As with SVNs, approximately 9-11% of the drug deposits in the lower respiratory tract[34,35] (Fig. 4[13]). However, grossly different from SVN (2%), about 80% of the drug from an MDI is deposited in the mouth and stomach.[34,35] With SVN, most of the large aerosol particles impact in the nebulizer and mouthpiece or mask because of the low velocity at which the aerosol moves. Thus, most of the drug is deposited in the apparatus (66%); whereas with MDIs, little is deposited in the apparatus (5-10%) because of the very high velocity of the MDI flow. As a result, side effects may be higher, especially with steroids, when MDIs without spacers are used.

Table 2 details a number of randomized, crossover studies demonstrating no significant difference in response between MDI without a spacer and SVN for various drugs in both asthmatic and COPD patients. However, it must be emphasized that in all of these studies each participant was capable of properly using the MDI. Proper use of an MDI without a spacer in the young and elderly is difficult, and it is probably this improper use that frequently results in unfavorable outcome.

Factors Affecting Efficacy

Much controversy exists over the technique that should be followed when an MDI is used. Differences of opinion exist over the lung volume at which the MDI should be actuated,[36-40] the position of the MDI in relationship to the mouth during actuation,[40-42] the length of a post-inhalation breathhold,[37,40-42] and the inspiratory flowrate.[36,37,40,43-45]

Lung Volume at Actuation. Concern regarding the lung volume at which the MDI should be actuated is based on the perceived need for peripheral distribution of the drug. Some have noted increased efficacy when actuation occurs early in an inspiratory capacity maneuver,[36,40] whereas others have demonstrated maximum effect when actuation occurs at 80% of vital capacity (VC). Newman et al[36] noted large increases in forced expiratory volume in the first second (FEV_1), peak expiratory flowrate (PEFR), maximum midexpiratory flowrate (MMEF), and instantaneous forced expiratory flow when the lung is at 50% of total lung capacity (TLC) ($\dot{V}_{max50\%}$) ($p < 0.01$) in 12 asthmatic patients when actuation occurred at 20% of VC as compared to 80% of VC. However, Riley et al[38] demonstrated improved FEV_1 ($p < 0.05$) when actuation occurred at 80% VC as opposed to 20% VC, but no difference was noted in specific airway con-

Table 2. Studies Comparing Patient Response to Bronchodilator via Small Volume Nebulizer vs Metered Dose Inhaler without Spacer

Investigators	Study Design	Patient Condition (n)	Drug	Evaluation	Results	Study Period
Mestitz et al[27]	Random, double-blind, placebo-controlled, crossover	Asthma (9)	Terbutaline	Spirometry, 6-min walk, symptom scores	NS*	4-weeks
Jenkins et al[28]	Random, double-blind, crossover	COPD (19)	Salbutamol	PEFR, spirometry, symptom score, extra beta-agonist use, exercise tolerance	NS	8-weeks
Cissik et al[29]	Random, double-blind, placebo-controlled, crossover	Asthma (10)	Isoetharine isoproterenol, metaproterenol, albuterol, terbutaline	Spirometry, PEFR	NS	2-weeks
Gunawardena et al[30]	Random, double-blind, placebo-controlled, crossover	COPD (32)	Ipratropium bromide	Spirometry, PEFR	NS	4-weeks
Shim & Williams[31]	Random, double-blind, crossover	Asthma(13) COPD (12)	Metaproterenol sulfate	FVC, FEV_1	NS	2-days
Gomm et al[32]	Random, crossover	Asthma (8) Bronchitis (2)	Ipratropium bromide	PEFR, spirometry, sG_{aw}	NS	2 days
Christensson et al[33]	Random, crossover	Asthma (20)	Salbutamol	Spirometry, MVV, single-breath N_2	NS	2 days

*NS = not significant.

ductance (s_{Gaw}) and $\dot{V}_{max50\%}$ between the two techniques. Those favoring actuation at higher volumes believe a more uniform peripheral distribution occurs at 80% VC than at 20% VC, whereas proponents of early actuation believe central airway deposition of the drug is enhanced with early actuation. Recent work by Dolovich et al[40] and Newman et al[37] suggests that the specific lung volume at which actuation takes place is unimportant, provided a slow maximal inspiration with a breath-hold is performed. We agree with these authors, because it is difficult to instruct patients to precisely control the lung volume at which they actuate the MDI. As noted in Table 3, actuation should occur near the beginning of a complete slow inhalation from functional residual capacity (FRC).

Table 3. Technique for Use of an MDI without Spacer

Warm MDI to body temperature.
Assemble apparatus.
Shake canister vigorously.
Hold canister upright.
Open mouth.
Place aerosol at mouth opening.
Begin to inspire slowly at inspiratory flows < 0.5 L/min.
Actuate MDI.
Continue to inspire to total lung capacity.
Hold breath for 4-10 seconds.
Wait 3-10 minutes between actuations.
Rinse mouth and pharynx if inhaling steroids.
Monitor patient for presence of side effects (eg, tachycardia or tremor) and beneficial effects (eg, improved breath sounds, peak flow, and FEV_1).

Inspiratory Flow. Inspiratory flow during MDI use also contributes to efficacy of therapy. Newman et al[37] demonstrated in 8 patients with reversible airway disease that a slow inspiration (25 L/min) improved FEV_1 to a significantly greater extent than 80 L/min inspiratory flow (Fig. 8). However, Williams[41] noted no difference in response to MDI inhalation between inspiratory flows of 30 L/min and 120 L/min if a breath-hold occurred after inspiration. Data from Dolovich et al,[40] Lawford and McKenzie,[42] Grainger,[43] and Woolf[44] support that of Newman et al.[37] suggesting that a slow inspiration maximizes the effect of MDI. The slow inspiration encourages laminar flow and deeper penetration of the aerosol before deposition.

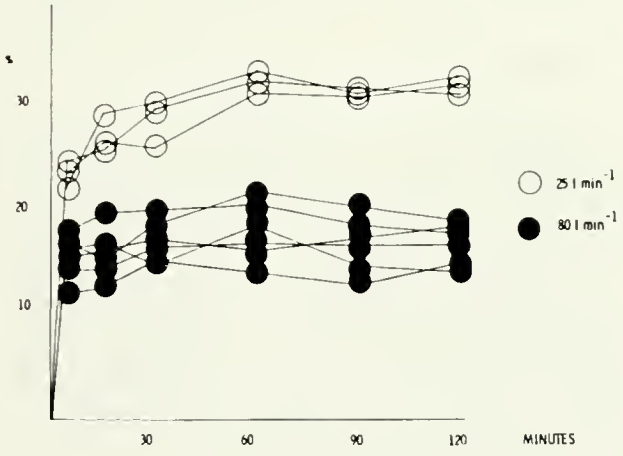


Fig. 8. Percentage increases in FEV_1, plotted against time following controlled inhalation of 500 μg terbutaline at 25 and 80 L/min peak inspiratory flow. Each patient performed 3 studies at 25 L/min and 6 studies at 80 L/min at various lung volumes and breath-holding pauses. (Reprinted, with permission, from Reference 37.)

Breath-Hold. After a complete inspiration, a breath-hold of 4-10 seconds should be encouraged. Data from both Dolovich et al[40] and Newman et al[37] indicate a 10-second hold is necessary. However, Lawford and McKenzie[42] (Fig. 9) in a placebo-controlled, crossover study of 11 patients with airflow obstruction noted no differences between a 4- and 10-second hold. It would seem logical that the longer the breath-hold, the greater the distribution and deposition of the inhaled drug. However, we believe that few patients with moderate-to-severe airflow obstruction are capable of a 10-second breath-hold after a slow maximum inspiration.

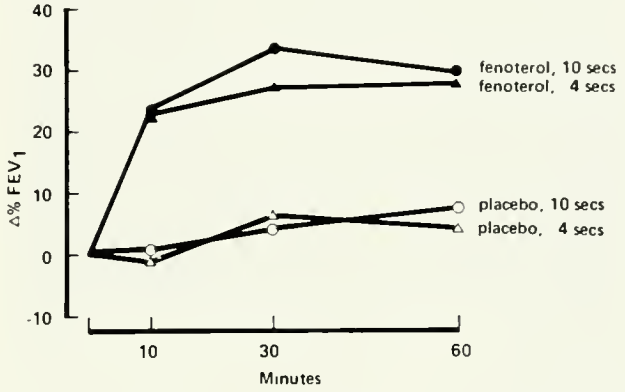


Fig. 9. Mean percent change in FEV_1 at 10, 30, and 60 minutes after 400 μg fenoterol hydrobromide inhalation by MDI or placebo with breath-holding times of 4 and 10 seconds. (Reprinted, with permission, from Reference 42.)

MDI Position. The position of the MDI in relationship to the patient's mouth has been studied by a number of groups. Dolovich et al,[40] in a study of 12 normal subjects, demonstrated that positioning the MDI 4 cm from the wide-open mouth resulted in the greatest percent deposition of the drug in the lung periphery. However, Lawford and McKenzie[42] noted no differences (Fig. 10) in 16 asthmatics with chronic airflow limitation with

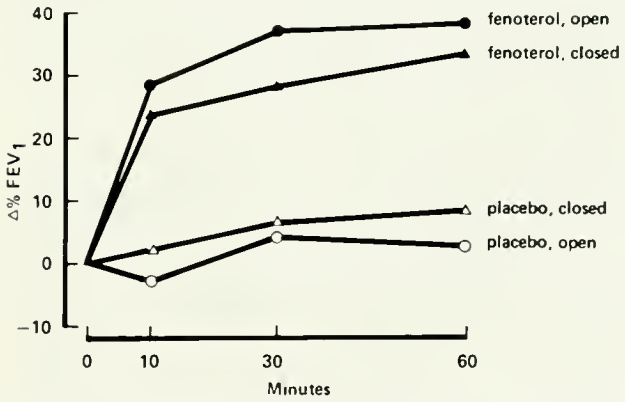


Fig. 10. Mean percent change in FEV, at 10, 30, and 60 min after 400 μg fenoterol hydrobromide inhalation by MDI or placebo via closed- or open-mouth technique. (Reprinted, with permission, from Reference 42.)

placement of the MDI between the lips versus 3 cm from the open mouth. Others[37,38,41] have also recommended MDI placement between the patient's lips. Based on the information currently available (1991), it is difficult to conclude which is the proper placement of the MDI. Inspiration with the MDI at a 4-cm distance from an open mouth may reduce potential side effects by decreasing oral deposition of large particles. However, it is difficult at best to consistently ensure that patients place the MDI in this position. In young and elderly patient groups, this position frequently results in the aerosol missing the mouth. As a result, we recommend placement of the aerosol at the entrance of the open mouth and not at a 4-cm distance from the mouth. In patients having difficulty with this position, closure of their lips around the MDI mouthpiece is encouraged.

Temperature. Temperature of the MDI prior to actuation also appears to affect percent deposition. Recently, Wilson et al[45] compared particle size produced and percent lower airway deposition in a lung model as temperature of the MDI varied between 0°C and 42°C. Their data indicated greater deposition (17.4% at 4°C and 32.2% at 37°C) and smaller MMAD (3.65 μm at 0°C and 2.50 μm at 37°C) if MDI canisters were warmed to 37°C before actuation. Prewarming of the MDI, particularly in winter, should be encouraged. Patients should be instructed to carry the MDI close to the body to maintain temperature or to prewarm by rolling the canister between their hands before actuation. The maintenance of the higher canister temperature increases canister vapor pressure, and results in smaller aerosol particle size.[46]

Timing of Actuations. Timing of sequential actuations enhances efficacy of the aerosol. Both Heimer et al[47] and Pedersen[48] noted greater bronchodilator response when individual actuations were separated by a period of time; they believed that the increased response resulted from the bronchodilating effect of the initial actuation's improving distribution of subsequent actuations. We recommend a 3- to 10-minute period between actuations, although in many patients a more practical interval is 1 minute.

Subject Instruction. As seen in Table 2, no difference in response from MDI and SVN has been demonstrated when MDI is properly administered. When one considers the detailed procedure required for proper administration of MDI (Table 3), it is not surprising that a number of authors have documented improper use of MDI.[49-54] This, we believe, is the primary reason for the varied response to MDI noted by the medical community. The need for careful detailed instruction to both patients and caregivers is essential if proper use of MDI is to be assured.[50,55-61] The problems with technique are most pronounced with the young and the elderly.[58,59] and require detailed individualized performance-based education[55-59,61] if proper use is to be assured. However, it should be emphasized that many patients may require a spacing device to ensure maximum benefit from an MDI.

Metered Dose Inhalers with Spacing Devices

Advantages

Spacing devices (also called auxiliary or accessory devices) are extensions to the MDI designed (1) to eliminate the need for hand-breath coordination, and (2) to greatly reduce the deposition of large aerosol particles in the upper airway.[62-64] These two effects of spacers eliminate the primary problems noted with MDI when compared to SVN. As already discussed, improper use of MDI is common, and a high percentage of the inhaled MDI-aerosol deposits in the oropharynx,[34,35] increasing systemic absorption and local side effects (oral thrush and suppression of adrenocortical activity with steroids).[64] Numerous studies[36,65-71] have demonstrated reduced oropharyngeal deposition with spacers. Kim et al[65] evaluated oropharyngeal and lung deposition with four spacing devices (Fig. 11) in a lung model at two inspiratory flowrates (0.33 and 0.83 L/s). Oropharyngeal deposition ranging from 33-71% with MDI alone was reduced to < 6% with all spacers. In addition, spacing devices increased lung deposition by as much as 38%, although the aerosol delivery with the smaller spacers (open tube and Aerochamber) was comparable to that obtained without the spacer. Corr et al.[66] also utilizing a lung model, determined the optimal

spacer to be 11 cm in length by 3.5 cm in diameter. With this spacer, Corr et al[66] noted stable particles of about 2.8 μm or smaller remained in suspension to be delivered to the lung. They suggested a two-stage process for the function of spacers: (1) impaction of large particles on the walls of the spacer and (2) evaporation's reducing particle size during residence in the space. Findings similar to those of Kim et al[65] and Corr et al[66] have been demonstrated by Newman et al.[67,68,71] In these studies, the use of a spacer reduced oropharyngeal deposition as much as 80% when compared with the MDI alone. In addition, these authors demonstrated higher deposition of the aerosol on the conducting airways when a spacer was used (11.2 ± 1.3% MDI vs 14.8 ± 1.4% with spacer;[68] 8.7 ± 1.8% MDI vs 20.9 ± 1.6% MDI with spacer[71]). Enhancement of spacer function with one-way valves has been noted by some authors[68,71] because the one-way valve increases the deposition of large particles in the spacer.

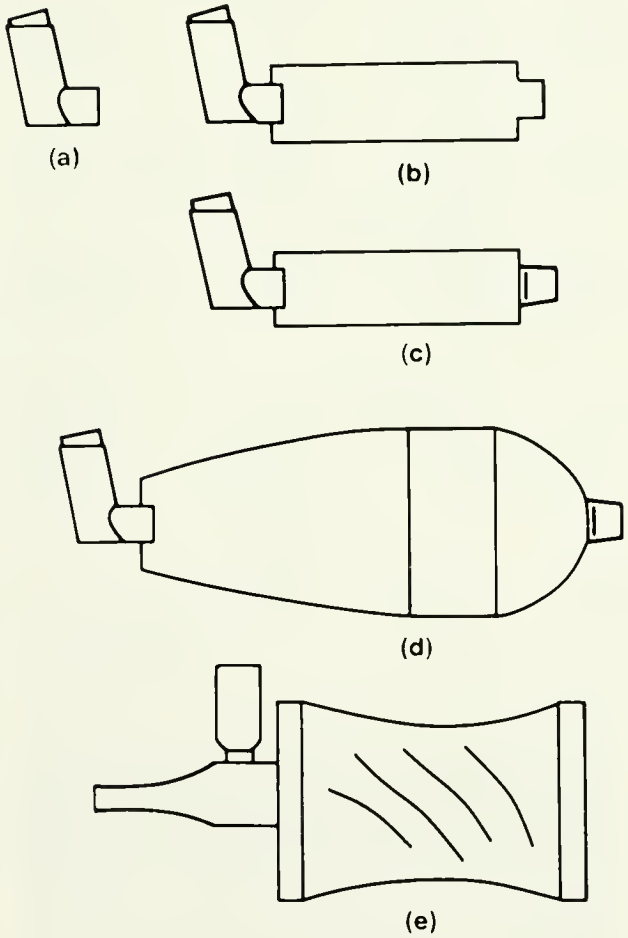


Fig. 11. Schematics of MDI spacer systems: (a) actuator alone, (b) open-end straight tube, (c) Aerochamber, (d) Nebuhaler and (e) InspirEase. (Reprinted, with permission, from Reference 65.)

Tables 4 and 5 list studies comparing the efficacy of MDI with spacers to MDI alone[40,72-81] and SVN.[82-91] As noted, MDI with spacer performs at least as well as MDI alone[40,72-81] or SVN[82-91] and outperform MDI when MDI technique is incorrect. MDI with spacer has also demonstrated equivalence to SVN in the emergency room[82,85,88] and during acute hospitalization.[82-84,88]

Technique

The technique for the use of an MDI with a spacer (Table 6) is essentially the same as with an MDI alone except that (1) after warming, shaking, and assembling the apparatus and positioning it for use, the MDI is actuated, after which inspiration begins; and (2) because inspiration should continue to TLC and because spacer volume is relatively small (normally less than 800 mL), a tight lip seal about the spacer is relaxed as inspiration continues, allowing for the inspiration of room air. As a result, a second inspiration from the spacer is recommended with some units (InspirEase) after an appropriate breath-hold. This assures that all of the aerosol from a single actuation is inspired. With other units (Aerochamber) this is not recommended. As with MDI alone, inspiration should be slow (< 0.5 L/s) and complete, beginning at FRC and continuing to TLC.

Metered Dose Inhalers versus Small Volume Nebulizers

Costs

In general, it is less expensive to use MDIs, even with a spacer, than to use SVN.[82,83,91] This is true whether patients are breathing spontaneously or are

Table 4. Studies Comparing Patient Response to Bronchodilator via Metered Dose Inhaler to Response via Inhaler with Spacer

Investigator	Study Design	Patient Condition (n)	Drug	Evaluation	Results	Study Period
Fairshter[72]	Random, crossover	Normal (12)	Metaproterenol	PEF	MDI-spacer > MDI	2 days
Crimi et al[73]	Random, crossover, double-blind	Asthma (13)	Albuterol	FEV_1	MDI-spacer > MDI	4 days
Lee & Evans[74]	Random, double-blind	Asthma (20)	Albuterol	FVC, FEV_1	If MDI technique correct, MDI-spacer = MDI; when MDI technique poor, FEV_1 with MDI-spacer > MDI	4 days
O'Reilly et al[75]	Random, crossover	Asthma (20)	Terbutaline	PEF, FEV_1	MDI-spacer > MDI	2 weeks
Fuller[76]	Random, crossover	Asthma (24)	Terbutaline	Spirometry, PEFR	NS	2 weeks
Morris et al[77]	Random, crossover	Asthma (8)	Terbutaline	FVC, FEV_1	MDI-spacer > MDI	2 days
Pauwels et al[78]	Random, crossover	Asthma (11)	Terbutaline	FEV_1, sG_{aw}, PEFR, $MEF_{75\%}$ $FEF_{75-85\%}$	MDI-spacer > MDI	2 days
Epstein et al[79]	Random, placebo-controlled, crossover	Asthma (13)	Fenoterol	FEV_1, FVC, PEFR	NS	4 days
Dolovich et al[40]	Random, crossover double-blind	Asthma (9)	Fenoterol	Spirometry, PEFR	NS	2 days
Fuglsang & Pedersen[80]	Random, placebo-controlled, crossover	Asthma (15)	Terbutaline	FEV_1	NS	4 days
Tobin et al[81]	Random, single-blind, crossover	Asthma COPD (10)	Metaproterenol	FEV_1, FVC, sG_{aw}	MDI-spacer > MDI	2 days

being mechanically ventilated. Jasper et al[83] demonstrated a $253,487 savings per year by using MDI with spacers in all non-ICU patients. In their analysis, they considered the cost of instruction in the use of an MDI to be $5.94, based on a single interaction. This is a relatively optimistic projection; however, even if the instructional cost were tripled, the cost saving would still be great ($205,769). Similar but more conservative cost savings were projected on a per week basis ($3,135) by Summer et al.[84] In Summer et al's analysis, a daily charge of $13.30 for instruction was included. Hess[92] describes much lower savings ($2.30 per treatment) when MDI is used on mechanically ventilated patients. The major factor affecting cost savings in mechanically ventilated patients is the extra labor required for MDI administration during mechanical ventilation.

When To Use an MDI, Spacer, or SVN

When efficacy, simplicity, and cost are considered, it is difficult to argue against the use of MDI in spontaneously breathing patients. However,

Table 5. Studies Comparing Patient Response to Bronchodilator via Small Volume Nebulizer vs Metered Dose Inhaler with Spacer

Investigators	Study Design	Patient Condition (n)	Drug	Evaluation	Results	Study Period /Comment
Salzman et al[82]	Random, double-blind, placebo-controlled	Asthma (44)	Metaproterenol	FVC, FEV_1	NS*	Acute severe exacerbation
Jasper et al[83]	Random, stratified to disease	Asthma/COPD (34)	Metaproterenol	FVC, FEV_1	NS	Equal acute hospital lengths of stay
Summer et al[84]	Random	Asthma/COPD (36)	Metaproterenol	FVC, FEV_1	NS	Equal acute hospital lengths of stay
Berry et al[85]	Random, double-blind, placebo-controlled	COPD (20)	Albuterol	FVC, FEV_1, Borg score	NS	Acute hospitalization
Turner et al[86]	Random, double-blind, placebo-controlled	Asthma/COPD (75)	Terbutaline	FEV_1, Borg score	NS	Acute severe exacerbation
Green & Jackson[87]	Random	COPD (60)	Terbutaline	PEFR	NS	Acute exacerbation
Gervais & Bégin[88]	Random, crossover	Asthma (10)	Salbutamol	FEV_1, FVC	NS	2 days
Berenberg et al[89]	Random	Bronchodilator ordered (100)	Metaproterenol	FEV_1, FVC, $FEF_{25-75\%}$	NS	Hospitalized for various reasons
Pederson & Bundgaard[90]	Random, crossover	Asthma (13)	Terbutaline	Flow-volume loops, FEV_1	NS	8 days
Cushley et al[91]	Random, placebo-controlled, crossover	Normal (8) Asthma (8)	Terbutaline	sG_{aw}, FEV_1	MDI-spacer > SVN for sG_{aw}, = for FEV_1	4 days

*NS = not significant.

careful analysis of each patient's ability must be made before specific decisions on device are made. Many patients do not use an MDI properly in spite of detailed instruction and careful supervision.[49-54] As a result, an MDI alone should be used only when proper technique is completely assured. Because most hospitalized patients are anxious and experiencing some physiologic stress, we recommend the use of a spacer unless they are experienced in the use of an MDI. A spacer should always be used when steroids are being delivered.

This information on MDIs leads one to question whether there is ever a role for SVN in spontaneously breathing patients, particularly because masks can be adapted to spacers for use in infants, children, and uncooperative adults. However, before attempts are made to totally eliminate SVN use in this setting, consider the inability of a distressed, uncooperative, or claustrophobic asthmatic or COPD patient to follow the ideal breathing pat-

Table 6. Technique for Use of Metered Dose Inhaler (MDI) with Spacer

Warm MDI to body temperature.
Shake canister vigorously.
Hold canister upright.
Actuate MDI.
Place mouthpiece in mouth.
Close lips about mouthpiece.
Inspire slowly (≤ 0.5 L/s) from spacer.
Continue to inspire to total lung capacity.
Hold breath 4-10 seconds.
Repeat inspiration with breath-hold if indicated by spacer manufacturer.
Wait 3-10 minutes between subsequent actuations.
Monitor patient for presence of side effects (eg, tachycardia or tremor) and beneficial effects (eg, improved breath sounds, peak flow, and FEV_1).

tern outlined in Table 6 when an MDI with spacer and mask is held to his or her face. Because of the ventilatory pattern established by patients in such settings, optimal MDI therapy may be impossible. Slow inspiration from FRC to TLC with a 4- to 10-second end-inspiratory hold does not occur. Thus, we would not discard the SVN but use it in those patients unable to achieve a ventilatory pattern resembling the ideal for use of MDI with spacer (Table 7).

Table 7. Patient Characteristics That May Make Use of a Small Volume Nebulizer Preferable to Metered Dose Inhaler with Spacer

Confused, disoriented
Extremely fatigued
Unable to master or tolerate MDI with spacer use, even with face mask
Experiencing severe, acute asthma.

Intermittent Positive-Pressure Breathing

Intermittent positive-pressure breathing (IPPB) can be used as a technique for the administration of aerosolized pharmacologic agents. However, evidence suggests that IPPB is no more effective than SVN or MDI for the administration of pharmacologic agents to stable patients with asthma or COPD.[90,93-97] The most convincing data are from the Intermittent Positive Pressure Breathing Trial Group multicenter study.[97] In that study, 985 patients were randomly assigned to SVN or IPPB with SVN and followed for an average of 33 months. No differences were noted in survival, FEV_1, forced vital capacity (FVC), FRC, P_{O_2}, or P_{CO_2} between the two groups. We must concur with the findings of these studies and the recommendations of others[98,99] that IPPB has no advantage over SVN or MDI for the administration of pharmacologic agents in patients with stable lung disease.

The data on the efficacy of IPPB during acute asthmatic attacks or acute exacerbation of COPD is somewhat more controversial, although some authors have demonstrated enhanced response with IPPB.[100-102] However, the dosage of the pharmacologic agent was 50-fold higher with IPPB compared to MDI in one of these studies.[102] Our own clinical experience has been negative regarding enhanced efficacy of drug delivery with IPPB in acute settings. The level of distress of the patient and the inability of available IPPB machines to meet the ventilatory demands of many patients have resulted in futile attempts to use IPPB. Thus, although the data are controversial, from a practical perspective we do not recommend the use of IPPB as a means of delivering aerosolized medication in any setting. However, IPPB may in some patients be indicated for reasons other than aerosol administration, which is beyond the scope of this review.

Dry Powder Inhalers

The use of DPI for the delivery of aerosolized pharmacologic agents is less common in the United States than MDI or SVN, although it has become commonplace for the delivery of certain agents in Europe. The DPI most frequently used in the United States is the Spinhaler[103] for the administration of cromolyn sodium, although the availability of cromolyn sodium in a liquid solution and MDI has probably lessened the use of the powdered form. The Spinhaler[103] and the Rotahaler,[104] used for the administration of albuterol and beclomethasone dipropionate, are single-dose devices. A multidose DPI, the Turbuhaler, is presently available in Europe for the administration of terbutaline sulfate.[105]

Advantages

The principal advantages of DPI are (1) they are breath-activated and require less patient coordination for proper use, and (2) they do not require the use of Freon as a propellant, with its associated environmental problems (see paper by Balmes in this issue[106]). The principal disadvantage of the single-dose devices is that they must be loaded with a capsule prior to each use. This is considered cumbersome and difficult to coordinate by some patients during acute exacerbations. In addition, with the Rotahaler, care must be taken not to tilt the device after the capsule is loaded and opened, to prevent loss of the drug.[107]

In contrast to SVN or MDI, inhalation of a DPI should be as rapid as possible,[107-109] because it is the inspiratory flow of the patient that creates the aerosol and moves the drug into the lung. However, efficacy has been demonstrated in patients unable to inspire rapidly.[105,110] Because the dry powder dissolves as it comes into contact with the mucosa, breath-holding is generally unnecessary,[107,109] although Auty et al[108] (in a group of 6 normal volunteers and 20 patients) noted an increased effect from sodium cromoglycate when a 10-second breath-hold was included in the administration protocol. As with MDI, inhalation should be from FRC to TLC (Table 8). When these protocols are followed, the percentage of the drug inhaled that deposits on the respiratory tract is about 13%,[109] similar to that deposited with MDI or SVN.

Table 8. Technique for Use with a Dry Powder Inhaler

Assemble apparatus.
Open capsule (technique specific for each device).
Exhale normally to functional residual capacity.
Place inhaler mouthpiece in mouth.
Seal lips around mouthpiece.
Inhale rapidly (> 60 L/min) through device, breath-hold unnecessary.
Repeat process until capsule is empty.
Rinse mouth after inhalation if medication is a steroid.
Monitor patient for presence of side effects (eg, tachycardia or tremor) and beneficial effects (eg, improved breath sounds, peak flow, and FEV_1).

Efficacy

Dry powder inhalers compare favorably to SVN[105,111,112] and MDI[110,113-121] (Table 9). In comparisons with asthmatic and COPD patients, essentially equivalent responses have been noted. The results of the most detailed of these studies is depicted in Fig. 12.[115] This study was a randomized, double-blind, placebo-controlled evaluation of 231 patients with asthma/COPD receiving albuterol, either by DPI or MDI. No differences in FEV_1, peak expiratory flow (PEF), or assessment of clinical efficacy were noted over a 12-week period.

Of the 13 studies reviewed in Table 9, in only one[112] did SVN therapy produce results greater than DPI—a study performed in children, in whom the question of proper technique must be considered. However, Muittari and Ahonen[120] noted a greater improvement in PEF in a group of asthmatic patients receiving salbutamol via DPI compared to MDI. In addition, the use of dry powder aerosols of salbutamol and terbutaline in high doses have been reported,[122-125] and albuterol as dry powder has also been shown to block exercise-induced bronchospasm.[126]

From data available, it appears that the DPI is as effective as the MDI and SVN in most clinical settings and may be used interchangeably. The primary limiting factor preventing more widespread use of DPI is its availability. Only terbutaline, salbutamol, beclomethasone dipropionate, and cromolyn sodium are available in powder form. Secondly, all delivery devices incorporate single-use capsules, except the Turbuhaler, for administration of terbutaline. This device (Fig. 13) contains 200 doses ready to inhale. In addition, the potential for side effects with steroids must be considered, because the required high inspiratory flows may increase oropharyngeal deposition of large particles. The only situations in which we would not recommend a dry powder are those in which we believe an SVN (Table 7) is superior to a DPI because of absence of patient cooperation. Table 10 contrasts the advantages and disadvantages of SVN, MDI, and DPI. As the result of increasing worldwide concern over the use of Freon and the worldwide ban on its use in the Year 2000, it seems reasonable to predict that DPI will become more common and available for the delivery of a greater variety of drugs, unless suitable alternatives to Freon become readily available. Guidance on the se-

Table 9. Studies Comparing Patient Response to Bronchodilator via Dry Powder Inhaler (DPI) vs Metered Dose Inhaler (MDI), Small Volume Nebulizer (SVN), or Tablets (T)

Investigators	Study Design	Technique	Patient Condition (n)	Drug	Evaluation	Results	StudyPeriod /Comment
Hansen[105]	Random, crossover	DPI vs SVN	Asthma/COPD (22)	Terbutaline	FEV_1, FVC	NS	2 days
Assoufi & Hodson[111]	Random	DPI vs SVN	Asthma/COPD (18)	Salbutamol	FEV_1, FVC, PEFR	NS	6 days, 3 doses compared
Grimwood et al[112]	Random, crossover	DPI vs SVN vs T	Asthma (17) children	Salbutamol	PEFR	SVN > DPI or T, $p < 0.01$	3 days over period 12-day
Johnsen & Weeke[113]	Random	DPI vs MDI	Asthma (9)	Terbutaline	FEV_1, FVC	NS	2 days, 2-9 days apart
Pover et al[114]	Random, double-blind, double-crossover, placebo-controlled	DPI vs MDI	Asthma (42)	Salbutamol	FEV_1	NS	3 days
Bronsky et al[115]	Random, double-blind, placebo-controlled	DPI vs MDI	Asthma/COPD (231)	Albuterol	FEV_1, FVC, $FEF_{25-75\%}$	NS	12 weeks
Persson et al[116]	Random, crossover	DPI vs MDI	Asthma (12)	Terbutaline	FEV_1, FVC	NS	2 days, at least 7 days apart
Tukiainen & Terho[110]	Random, double-crossover	DPI vs MDI	Asthma (22)	Salbutamol	PEFR	NS	3 days
Sovijarvi et al[118]	Random	DPI vs MDI	Asthma (29)	Salbutamol	FEV_1, PEF, FVC, $FEF_{25-75\%}$	NS	1 day, induced bronchospasm
Edmunds et al[119]	Random, double-blind, crossover	DPI vs MDI	Asthma (14) children	Beclomethasone dipropionate	PEFR	NS	2 months
Swinburn & Sexton[117]	Random, crossover	DPI vs MDI vs MDI-spacer	Asthma (12)	Salbutamol	PEFR	NS	24 days
Muittairi & Ahonen[120]	Crossover	DPI vs MDI	Asthma (14)	Salbutamol	PEFR	DPI > MDI $p < 0.05$	6 weeks
Smith & Gwynn[121]	Random, crossover	DPI vs MDI	Asthma (37)	Beclomethasone dipropionate	PEFR	NS	8 weeks

*NS = no significant difference.

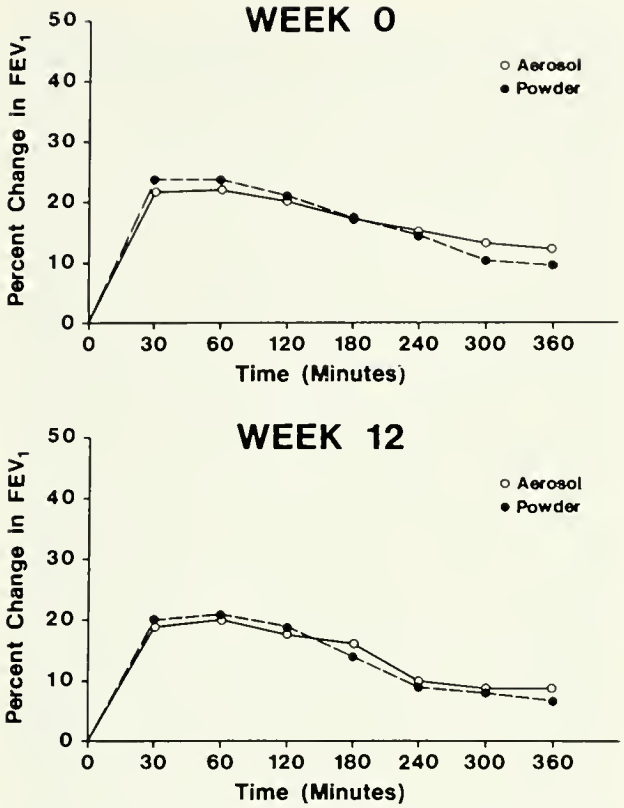


Fig. 12. Comparison of effect of albuterol administered by MDI or DPI. Week 0 percent-change from baseline in mean FEV_1 after treatment with albuterol by DPI (n = 115) or MDI (n = 116). Week 12 data identical to that obtained at Week 0 after treatment with albuterol by DPI (n = 89) or MDI (n = 94). No differences were noted between the MDI and DPI. (Reprinted, with permission, from Reference 115.)

lection of appropriate aerosol delivery devices is provided in Table 11.

Aerosol Therapy during Mechanical Ventilation

Aerosol therapy may be administered during mechanical ventilation by either SVN or MDI. However, no descriptions of the use of DPI aerosols during mechanical ventilation are available because DPIs are breath-activated and require rapid inspiratory flows. Assurance of predictable drug dosing during mechanical ventilation is more limited than during spontaneous breathing because of loss of aerosolized drugs in ventilator circuits and the presence of artificial airways that act as barriers to the entrance of aerosols into the lung.

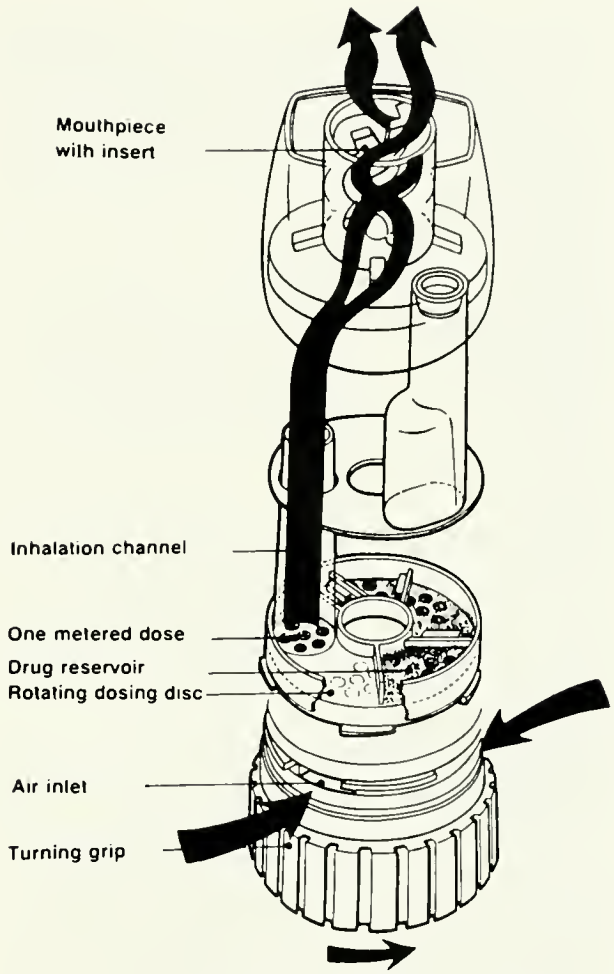


Fig. 13. Turbuhaler for the administration of terbutaline. This device contains 200 individual doses ready to inhale. (Reprinted, with permission, from Reference 116.)

Small Volume Nebulizers

Factors Affecting Delivery and Deposition

Aerosolization of pharmacologic agents through mechanical ventilator circuits has been therapeutically employed since the early 1960s.[127,128] However, only recently has actual data on drug delivery via this approach become available. During spontaneous inspiration with SVN therapy, about 8-12% of the drug placed in the nebulizer deposits in the respiratory tract.[12,13] During mechanical ventilation, the efficiency of aerosol deposition is decreased to a greater extent than during spontaneous breathing.[23,129-133] Numerous factors contribute to this inefficiency, including endotracheal-tube

Table 10. Advantages and Disadvantages of the Use of Small Volume Nebulizers (SVN), Metered Dose Inhalers (MDI), and Dry Powder Inhalers (DPI)

Advantages	Disadvantages
SVN	
Less patient coordination required	Expensive
High doses possible (even continuous)	Wasteful
No chlorofluorocarbon release	Contamination possible if not carefully cleaned
	Not all medications available
	Pressurized gas source required
	More time required
MDI	
Convenient	Patient coordination required
Inexpensive	Patient activation required
	Results in pharyngeal deposition
	Has potential for abuse
	Difficult to deliver high doses
	Not all medications available
	Dependent on ozone-depleting chlorofluorocarbons
MDI with Auxiliary Device	
Less patient coordination required	More complex process for patient who can use MDI alone
	More expensive than MDI alone
	Less portable than MDI alone
DPI	
Less patient coordination required	Requires high inspiratory flow
	Most units are single dose
Breath-hold not required	Can result in pharyngeal deposition
No chlorofluorocarbon release	Cannot be used with intubated patients
Breath-activated	Not all medications available
	Difficult to deliver high doses

size,[130] MMAD of aerosol particles,[130] continuous vs intermittent nebulization,[23,131,132] and placement of the nebulizer in the ventilator circuit.[23] MacIntyre et al[129] in a group of 7 stable, adult, mechanically ventilated patients reported that 2.9 ± 0.79% of a radioactively tagged aerosol was deposited in the lower respiratory tract. Fraser et al,[133] using a lung model and SVN activation during inspiration, noted that only 4.8% of the initial dose was available for deposition in the large airways.

Airway Diameter. Evaluation of aerosol deposition in neonatal and pediatric lung models has demonstrated even less deposition than that noted with adults.[131,134,135] Cameron et al[131] noted a maximum of 1.52% of the generated aerosol deposited in a lung model used to evaluate the function of five SVNs in a neonatal ventilator circuit. The model used consisted of a 3.5-mm-ID endotracheal tube, a filter for aerosol particle impaction, and a rubber test lung. Throughout the evaluation, all nebulizers were powered by 6-8 L/min oxygen and a solution volume of 4 mL was used, with the test lung ventilated at a peak airway pressure of 20 cm H_2O with 2 cm H_2O PEEP, an I:E of 1:1, and a respiratory rate of 30/min. Flavin et al[134] reported similar findings in a rabbit model. All rabbits in that study were intubated with a 3.0-mm-ID endotracheal tube and ventilated with a Bourns LS-104 ventilator. A radioactive aerosol was used and three nebulizers were evaluated. A maximum of 1.96 ± 1.19% of the aerosol was deposited in the lower respiratory tract of the rabbits. Cameron et al,[135] also using a rabbit model, noted 2.8% of the aerosol produced deposited in the rabbit lung during conventional time-cycled, pressure-limited ventilation (peak pressure 30 cm H_2O, PEEP 2 cm H_2O, rate 30/min, I:E 1:1, and gas flow 8 L/min). Percent deposition decreased as peak airway pressure, tidal volume, and inspiratory time decreased.

Endotracheal-Tube Size. The effect of endotracheal-tube size on percent deposition was demonstrated in a lung model by Ahrens et al.[130] Using 0.1% uranine as a tracer, they demonstrated a decrease in percent deposition as endotracheal-tube size decreased from 9-mm to 6-mm to 3-mm ID. They also noted enhanced lung-model deposition as the MMAD of the aerosol particles was reduced. Maximum deposition beyond the tip of the 3-mm-ID tube was noted when a MMAD of 0.54 μm was delivered.

Nebulizer Operation and Position. Volume of aerosol deposited in the lung can be increased by

Table 11. Considerations in Choosing a Specific Aerosol Delivery Device

Primary device of choice is metered dose inhaler (MDI).
If patient is unable to use MDI properly, use MDI with spacer or dry powder inhaler.
If very high doses or continuous use is required or if patient does not tolerate MDI with spacer, use small volume nebulizer.

placement of the SVN at least 18 inches from the endotracheal tube.[23] Hughes and Saez evaluated the amount of aerosol presented to the endotracheal tube of a lung model under four conditions:[23] (1) continuous nebulization at the patient Y, (2) intermittent nebulization at the Y, (3) continuous nebulization at the ventilator-circuit manifold, and (4) intermittent nebulization at the ventilator-circuit manifold. The highest percentage of aerosol presented to the endotracheal tube (68.3 ± 1.2%) occurred during intermittent nebulization at the manifold (Fig. 14), whereas the lowest percentage (30 ± 2.0%) occurred during continuous nebulization at the Y. Others have also recommended intermittent nebulization,[132,133] whereas Dählback et al[136] have recommended nebulization at the manifold only during exhalation. Because 61.0 ± 1.5% of the aerosol was delivered during continuous nebulization at the manifold in the study by Hughes and Saez,[23] it appears that nebulizer location is the most critical variable, with intermittent nebulization having a lesser effect.

Fig. 14. Placement of an SVN at the manifold of a ventilator circuit.

Efficacy

MacIntyre et al[129] questioned the efficacy of SVN therapy administered during mechanical ventilation because of the presence of the endotracheal tube and suboptimal breathing patterns during therapy. In a series of 15 patients, they noted no change in heart rate, peak airway pressure, inspiratory airway resistance, or expiratory flow at 50% of vital capacity. However, Gay et al,[137] in a series of 10 dynamically hyperinflated, mechanically ventilated patients, noted a 21-50% increase in expiratory flow at a respiratory system recoil pressure of 6 cm H_2O, a mean decrease in peak airway pressure of 4.7 cm H_2O, and intrinsic PEEP of 2.4 cm H_2O, and a 200-mL reduction in end-expiratory lung volume. As in the study of MacIntyre et al,[129] Gay et al[137] used a standard dose of metaproterenol sulfate, and attached the nebulizer at the Y-piece of the ventilator circuit. In spite of the very low percentage of SVN aerosol deposited in the lower respiratory tract in infants, both Brudno et al[138] and Wilkie and Bryan[139] noted improvements in inspiratory and expiratory resistance, compliance, and tidal volume during pressure-limited ventilation in infants with bronchopulmonary dysplasia. Two factors are apparent from these studies and the data on deposition of aerosol in the lung: (1) dosage of drug administered via SVN needs to be increased over standard recommendations if the same quantity of drug is to reach the respiratory tract as during spontaneous inhalation without an artificial airway, and (2) inspiratory resistance may not be the ideal variable to monitor in order to establish response to therapy due to the presence of an artificial airway. Peak airway pressure, intrinsic (auto) PEEP level, and expiratory flows and resistance appear to provide a better evaluation of efficacy.

Technique

In spite of the fact that little specific information is available regarding the optimal technique for the use of SVN via ventilator circuits, the data from Hughes and Saez[23] and the information presented earlier on SVN technique during spontaneous breathing (Table 1) allow us to establish guidelines for the use of SVNs in ventilator circuits (Table

12). All SVNs should be placed at least 18 inches from the Y (Fig. 14) and powered intermittently through the ventilator (if possible). The volume of solution nebulized should be 4 mL; and if powered by a gas source external to the mechanical ventilator, a flow of 6-8 L/min should be used.

Table 12. Technique for Use of Small Volume Nebulizer during Mechanical Ventilation

Place drug in nebulizer.
Dilute with physiologic saline (0.9%) to 4 mL total volume.
Insert nebulizer into inspiratory limb of ventilator circuit at least 18 inches from Y.
Use intermittent nebulizer flow from ventilator if available.
If continuous flow is used, set at 6-8 L/min.
Set ventilator rate at 4-8/min or higher if not contraindicated.
Set tidal volume at 12 mL/kg or more unless contraindicated. If PSV rate drops, add backup SIMV rate.
With children, adjust ventilator flow to assure that total flow is unchanged during pressure-limited ventilation.
With children (and some adults), readjust tidal volume during continuous-flow nebulization to maintain constant tidal volume and peak airway pressure.
Tap sides of nebulizer to minimize dead volume.
Continue treatment until no aerosol is produced.
Remove equipment from ventilator circuit.
Return ventilator to pretreatment settings.
Monitor patient for presence of side effects (eg, tachycardia or tremor) and beneficial effects (eg, improved breath sounds, peak flow, and FEV_1).

During administration of SVN to spontaneously breathing patients, a periodic deep breath and a breath-hold are recommended[26] (Table 1). Although we realize that this may be impossible for many mechanically assisted patients, it is encouraged. In order to maximize distribution and establish a more ideal ventilatory pattern during SVN treatments, we recommend the delivery of volume-limited mechanical breaths at a rate of 4-8/min or more, with tidal volumes set at 12 mL/kg or greater, unless contraindicated in a given patient. Patients on CPAP should be changed to synchronized intermittent mandatory ventilation (SIMV) or assist/control (A/C) during therapy, and patients receiving pressure support ventilation (PSV) with an SIMV backup rate of less than 8/min should have the PSV trigger-rate carefully monitored. If PSV rate decreases, a backup SIMV rate of 8/min should be set. As noted by Beaty et al,[140] the use of continuous-nebulizer flow increases the pressure gradient patients must overcome to trigger pressure support ventilation. In those patients with marginal respiratory efforts, gross hypoventilation has been noted.

When continuous nebulization is used, the gas powering the nebulizer increases the mechanically delivered tidal volume and peak airway pressure. This is normally not a concern in most adults, but may create important problems in children. With children (and some adults), delivered tidal volume should be decreased to ensure consistency during aerosol therapy. During continuous-flow pressure-limited ventilation in neonates and children, the flow from the ventilator must be reduced by a level equivalent to the added continuous-nebulizer flow. If this adjustment is not made, peak airway pressure and delivered tidal volume may increase.

As with spontaneously breathing patients, dead volume should be minimized by tapping the sides of the SVN to allow nebulization of solution adhering to the walls of the SVN. Nebulization should be continued until no aerosol is produced. Finally, nebulizers should be changed daily to ensure that bacterial contamination of the airway is minimized.[141]

Metered Dose Inhalers

Early Applications

MDIs have been used to administer aerosolized medication during anesthesia since the 1960s.[142-144] Most of these early reports were simply descriptions of methodology. However, Fresoli et al[144] described the use of isoproterenol in eight patients requiring bronchodilatation during anesthesia. They affixed the MDI adapter between the Y of the anesthesia circuit and the endotracheal tube, and administered the MDI during a mechanical inspiration. As many as eight actuations were required to elicit the desired response.

In 1975, Gold[145] reported the use of isoproterenol in 12 intubated and anesthetized patients with bronchospasm. Their positioning of the MDI was the same as Fresoli et al;[144] however, a manual ventilator was used during actuation. After two ac-

tuations, peak airway pressure decreased from 43 ± 2 torr to 31 ± 2 torr, and P_{CO_2} decreased from 60 ± 6 torr to 47 ± 4 torr. Sprague[146] reported similar, although less dramatic results, with an isoetharine and phenylephrine mixture. After up to six actuations from the MDI, administered with an end-inspiratory hold of 3 seconds, a mean decrease in peak airway pressure of about 4 cm H_2O was observed, with individual patients demonstrating a 6 cm H_2O drop. Additional anecdotal reports of MDI use in anesthesia have been provided through the 1980s.[147-151] In spite of the significant attention MDIs have received in anesthesia for the last 25 years, only recently has interest in the use of MDI during mechanical ventilation peaked.

Airway Deposition

As with SVNs, the addition of an artificial airway decreases the quantity of MDI-delivered drug that deposits in the lower respiratory tract.[152-155] As noted earlier, about 9-11%[34,35] of the drug from an MDI is deposited in the lower respiratory tract in spontaneously breathing patients. While limited,[152-155] data available on deposition beyond the distal tip of the endotracheal tube indicate (at maximum) about 50% less deposition than during spontaneous breathing, or 4-6% of the actuated aerosol exits the endotracheal tube.

In a bench study on the effects of variation in ventilatory pattern and endotracheal-tube size, Hess et al[152] noted an overall 3.3 ± 2.1% of the aerosol deposited in a filter beyond the endotracheal tube. An average of 89.2 ± 3.8% of the aerosol deposited on the endotracheal tube, and 7.4 ± 3.2% deposited on the MDI adapter. No differences in percentage of deposition were noted as flowrate (30 and 60 L/min), tidal volume (0.5 and 1.5 L), or endotracheal-tube size (7.0 and 9.0 mm) changed. However, Crogan and Bishop,[153] also using a lung model, noted a greater percentage of the aerosol exiting the endotracheal tube as size increased (3.0 ± 1.9% for a 6.0-mm tube, and 6.5 ± 4.4% for a 9.0-mm tube). They also noted a greater quantity of aerosol exiting the endotracheal tube if actuation occurred just after the start of a mechanical tidal-volume delivery than if actuation began before onset of the mechanical breath.

In a randomized comparison of SVN and MDI, Fuller et al[154] demonstrated 5.65 ± 1.09% of the aerosol delivered by MDI, compared to 1.22 ± 0.35% by SVN deposited in the lower respiratory tract. In this study, 4 puffs of radiolabeled fenoterol were delivered, with actuations spaced 5 minutes apart. Fuller et al[155] also noted no statistically significant differences between deposition from MDI with endotracheal tubes (4.58 ± 3.03%) or tracheostomy tubes (6.69 ± 2.80%) in a series of mechanically ventilated patients.

SVN vs MDI Efficacy

Little data comparing the efficacy of SVN and MDI during mechanical ventilation are available.[156-158] Recently, Gay et al[156] demonstrated no differences between the administration of 270 μg (3 puffs via MDI) and 2.5 mg in a 3.5-mL-solution volume (SVN) of albuterol. Changes in passive expiratory flow at respiratory system recoil pressures of 6-10 cm H_2O were the same in both arms of this single-blind, randomized crossover comparison. Similar results have been provided in abstracts by Hess et al[157] and Gutierrez and Nelson[158] in series of mechanically ventilated patients, whereas Fernandez et al[159] noted no differences between the effects of MDI-administered ipratropium bromide or salbutamol and intravenous aminophylline in a series of 20 mechanically ventilated COPD patients. In spite of the limited data comparing these techniques in mechanically ventilated adults and older children, we feel confident in concluding that SVN and MDI therapy are equivalent in mechanically ventilated patients, because extensive data (Tables 2 and 4) establishing equivalence in spontaneously breathing subjects are available. At this time, insufficient data are available to allow recommendations regarding MDI in neonates, infants, and small children who are mechanically ventilated.

MDI Adapters

Adapters designed to interface MDIs with the ventilator circuit can be classified as (1) modified tracheal swivel adapters (Fig. 15); (2) circuit inspiratory-limb adapters (Fig. 16); and (3) circuit inspiratory-limb spacers (Fig. 17). Specifics regarding

Fig. 15. MDI and modified tracheal swivel adapter.

Fig. 16. MDI and circuit inspiratory-limb adapter.

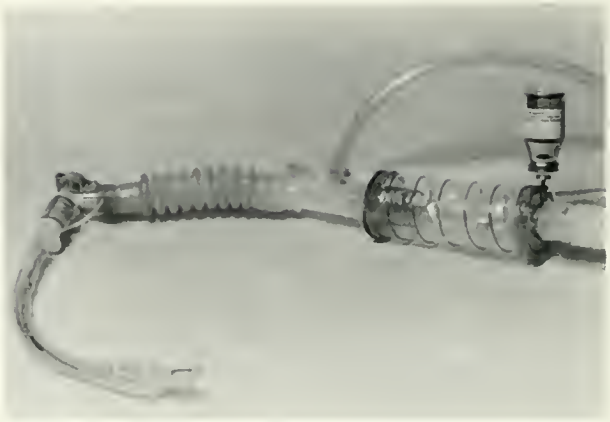


Fig. 17. MDI and circuit inspiratory-limb spacer (AeroVent). (A) Spacer with MDI ready for use. (B) Spacer closed as exists in-line when not in use.

available adapters have been recently reviewed by Hess.[92] However, little data are available to determine which of the adapters is most effective in depositing aerosol beyond the distal tip of the endotracheal tube and producing maximum patient response. Bishop et al[160] demonstrated, in a lung model, that a larger volume of particles in the "respiratory range" (1-5 μm) was delivered beyond the endotracheal tube with the Monaghan AeroVent, as compared to the Intermedical Intec 172275 and Instrumentation Industries RTC-22. More recently, catheters extending to the tip of the ET tube have been used by Taylor and Lerman[161] and Peterfreund[162] to increase the delivery of metered-dose drugs beyond the endotracheal tube. Taylor and Lerman,[161] in a lung model, demonstrated delivery of 97% of actuated salbutamol beyond the ET tube when a 19-gauge catheter attached to the MDI was positioned at the tip of the ET tube. Also using a lung model, Peterfreund[162] demonstrated that the use of a 16-gauge, 12-inch intravenous catheter attached to the MDI, positioned in a tracheal swivel adapter, resulted in delivery of 20% of the MDI-generated aerosol beyond the ET tube. These preliminary data suggest an exciting alternative for MDI delivery in intubated patients, but additional research is required before application. The data available on the placement of MDI in ventilator circuits are too limited at this time to allow a recommendation to be made on the best approach. Additional studies need to be performed before guidelines can be presented.

Technique for Use of MDI in Ventilator Circuits

Little information derived specifically from evaluation of MDI use during mechanical ventilation is available to assist in defining the ideal technique for MDI administration. However, it seems

reasonable to extrapolate from the abundant information available on the use of MDI during spontaneous breathing. During mechanical ventilation, Gay et al[156] administered the MDI during a large-volume manual inflation with a breath-hold of several seconds, waiting 1 minute between actuations. Fernandez et al[159] recommend a large, slowly delivered tidal volume by manual ventilator, with a 10-second breath-hold and a 5-minute wait between actuations. However, Hess et al[152] noted no difference in drug deposition based on tidal volume or peak inspiratory flow, whereas Crogan and Bishop[153] found a flow of 60 L/min most efficient.

Based on this information, we present preliminary guidelines for MDI administration during mechanical ventilation in Table 13. Ideally, a large tidal volume delivered at moderate flowrates of 30-60 L/min and held in the airway for at least 2-3 seconds is recommended. Whether this ventilatory pattern should be performed by manual or mechanical ventilation has not been determined. As with spontaneously breathing, non-intubated patients, a pause between actuations is probably ideal, although this has not been studied extensively. Unless a true in-line spacer is used (AeroVent), actuation of the MDI should occur immediately after the beginning of a mechanical breath. If the AeroVent is used, actuation should occur 1-2 seconds before the beginning of the mechanical breath or at the end of exhalation, depending on patient-ventilator rate.

Table 13. Technique for Use of Metered Dose Inhaler (MDI) during Mechanical Ventilation

Place MDI adapter into circuit.
Adjust ventilator to deliver volume-limited breaths or use a manual ventilator.
Warm MDI to body temperature.
Shake MDI vigorously.
Place MDI in circuit.
Actuate MDI immediately after the beginning of a mechanical breath; if spacer is used, actuate 1-2 seconds before mechanical breath or near end-exhalation, depending on the rate.
Apply a 2-3-second inflation hold, if not contraindicated.
Wait 1 minute between actuations.
Return ventilator to pretreatment settings.
Monitor patient for presence of side effects (eg, tachycardia or tremor) and beneficial effects (eg, improved breath sounds, peak flow, and FEV_1).

Dosing during Mechanical Ventilation

As has been indicated, the percentage of drug deposited beyond the endotracheal tube with either MDI[152-155] or SVN[23,130-134] is about 50% or less of that deposited during spontaneous breathing. As a result, and as has been demonstrated in the studies reviewed here, a larger dose of bronchodilator should be administered during mechanical ventilation than during spontaneous breathing if equivalent deposition in the lower respiratory tract is desired. As a general rule, we recommend a doubling of the standard dose used in spontaneously breathing patients (that is, 4 puffs from most MDIs and approximately 0.6-1 mL of most SVN drug solutions dependent upon specific drug). However, we caution that actual dosing should be further modified based on patient response, and we find that many patients require and safely tolerate much higher doses than we have recommended as standards.

Prospectus

The scientific basis for the delivery of aerosol therapy has increased markedly over the last 10 years. This has allowed us to firmly establish guidelines for the administration of aerosolized pharmacologic agents to spontaneously breathing patients. Although research is still needed, the scientific basis for delivery during spontaneous breathing greatly exceeds the knowledge-base for delivery during mechanical ventilation. Although we have extrapolated guidelines from spontaneous breathing data, as described here, little direct information is available to guide our delivery of aerosolized drugs to patients requiring ventilatory assistance. As has been pointed out by Hess,[92,163] enormous research opportunities exist and numerous questions regarding application, methodology, and dosing need to be answered.

We hope that this review has not only clarified issues and helped establish guidelines, but will also provide the stimulus for respiratory care practitioners to design research proposals to answer the questions that still exist in this important facet of respiratory care.

REFERENCES

1. Clay MM, Pavia D, Newman SP, Lennard-Jones T, Clarke SW. Assessment of jet nebulisers for lung aerosol therapy. Lancet 1983;2:592-594.

2. Hess D, Horney D, Snyder T. Medication-delivery performance of eight small-volume, hand-held nebulizers: effects of diluent volume, gas, flowrate, and nebulizer model. Respir Care 1989;34:717-723.
3. Wood JA, Wilson RSE, Bray C. Changes in salbutamol concentration in the reservoir solution of a jet nebulizer. Br J Dis Chest 1986;80:164-169.
4. Clay MM, Pavia D, Newman SP, Clarke SW. Factors influencing the size distribution of aerosols from jet nebulisers. Thorax 1983;38:755-759.
5. Douglas JG, Leslie MJ, Brompton GK, Grant IW. Is the flow rate used to drive a jet nebuliser clinically important? (letter). Br Med J Clin Res 1985;290:29.
6. Kradjan WA, Lakshminarayan S. Efficiency of air compressor-driven nebulizers. Chest 1985;87:512-516.
7. Suez D, Chai H. A standard method of intermittent inhaled therapy via a jet nebulizer. Ann Allergy 1986; 57:245-248.
8. Johnson MA, Newman SP, Bloom R, Talaee N, Clarke SW. Delivery of albuterol and ipratropium bromide from two nebulizer systems in chronic stable asthma: efficacy and pulmonary deposition. Chest 1989;96:6-10.
9. Newman SP, Pellow PGD, Clarke SW. In vitro comparison of DeVilbiss jet and ultrasonic nebulizers. Chest 1987;92:991-994.
10. Phipps PR, Gonda I. Droplets produced by medical nebulizers: some factors affecting their size and solute concentration. Chest 1990;97:1327-1332.
11. Porstendofer J, Gebhart J, Robig G. Effects of evaporation on the size distribution of nebulized aerosols. J Aerosol Sci 1977;8:371-380.
12. Newman SP. Aerosol deposition considerations in inhalation therapy. Chest 1985;88(2, Suppl):152S-160S.
13. Lewis RA, Fleming JS. Fractional deposition from a jet nebulizer: how it differs from a metered dose inhaler. Br J Dis Chest 1985;79:361-367.
14. Massey DG, Miyauchi D, Fournier-Massey G. Nebulizer function. Bull Eur Physiopathol Respir 1982;18: 665-671.
15. Arossa W, Quagliotti F, Sala N, Spinaci S, DeCandussio G. Different performance of two commercial nebulizers. Respiration 1984;46:128-132.
16. Hadfield JW, Windebank WJ, Bateman RM. Is driving gas flow rate clinically important for nebulizer therapy? Br J Dis Chest 1986;80:50-54.
17. Davis SS. Physio-chemical studies on aerosol solutions for drug delivery: I. Water-propylene glycol systems. Int J Pharm 1978;1:71-83.
18. Mercer T. Production of therapeutic aerosols. J Aerosol Sci 1977;8:371-380.
19. Heyder J. Mechanism of aerosol particle deposition. Chest 1981;80:820-823.
20. Leiberman A, Ohki M, Forte V, Fraschetti J, Cole P. Nose/mouth distribution of respiratory airflow in mouth breathing children. Acta Otolaryngol (Stockh) 1990; 109:454-460.
21. Steventon RD, Wilson RS. Facemask or mouthpiece for delivery of nebulized bronchodilator aerosols? Br J Dis Chest 1981;75:88-90.
22. Wood DO, Chandler D, Dugdale AE. Two methods of administering nebulised salbutamol, a controlled study. Aust Paediatr J 1978;14:150-155.
23. Hughes JM, Saez J. Effects of nebulizer mode and position in a mechanical ventilator circuit on dose efficiency. Respir Care 1987;32:1131-1135.
24. Pavia D, Thompson ML, Clarke SW, Shannon HS. Effect of lung function and mode of inhalation on penetration of aerosol in the human lung. Thorax 1977;32:194-197.
25. Dolovich M, Ryan G, Newhouse MT. Aerosol penetration into the lung: influence on airway responses. Chest 1981;80:834-836.
26. Newman SP, Woodman G, Clarke SW. Deposition of carbenicillin aerosols in cystic fibrosis: effects of nebuliser system and breathing pattern. Thorax 1988;43: 318-322.
27. Mestitz H, Copland JM, McDonald CF. Comparison of outpatient nebulized vs metered dose inhaler terbutaline in chronic airflow obstruction. Chest 1989;96:1237-1240.
28. Jenkins SC, Heaton RW, Fulton TJ, Moxham J. Comparison of domiciliary nebulized salbutamol from a metered-dose inhaler in stable chronic airflow limitation. Chest 1987;91:804-807.
29. Cissik JH, Bode FR, Smith JA. Double-blind cross-over study of five bronchodilator medications and two delivery methods in stable asthma. Chest 1986;90:489-493.
30. Gunawardena KA, Smith AP, Shankleman J. A comparison of metered dose inhalers with nebulizers for the delivery of ipratropium bromide in domiciliary practice. Br J Dis Chest 1986;80:170-178.
31. Shim CS, Williams MH Jr. Effect of bronchodilator therapy administered by canister versus jet nebulizer. J Allergy Clin Immunol 1984;73:387-390.
32. Gomni SA, Keaney NP, Hunt LP, Allen SC, Stretton TB. Dose response comparison of ipratropium bromide from a metered dose inhaler and by jet nebulization. Thorax 1983;38:197-301.
33. Christensson P, Arborelius M, Lilja B. Salbutamol inhalation in chronic asthma bronchiale: dose aerosol vs jet nebulizer. Chest 1981;79:416-419.
34. Newman SP, Pavia D, Morén F, Sheahan NF, Clarke SW. Deposition of pressurized aerosols in the human respiratory tract. Thorax 1981;36:52-55.
35. Spiro SG, Singh CA, Tolfree SEJ, Partridge MR, Short MD. Direct labelling of ipratropium bromide aerosol and its deposition pattern in normal subjects and patients with chronic bronchitis. Thorax 1984;39:432-435.
36. Newman SP, Pavia D, Bateman RM, Clarke SW. Bronchodilator response after administration of pressurized aerosols at different lung volumes in patients with airway obstruction (abstract). Clin Sci 1979;56:10P-11P.

37. Newman SP, Pavia D, Clarke SW. Simple instructions for using pressurized aerosol bronchodilators. J Royal Soc Med 1980;73:776-779.
38. Riley DJ, Weitz BW, Edelman NH. The responses of asthmatic subjects to isoproterenol inhaled at differing lung volumes. Am Rev Respir Dis 1976;114:509-515.
39. Riley DJ, Liu RT, Edelman NH. Enhanced responses to aerosolized bronchodilator therapy in asthma using respiratory maneuvers. Chest 1979;76:501-507.
40. Dolovich M, Ruffin RE, Roberts R, Newhouse MT. Optimal delivery of aerosols from metered dose inhalers. Chest 1981;80(Suppl):911S-915S.
41. Williams TJ. The importance of aerosol technique: does speed of inhalation matter? Br J Dis Chest 1982;76:223-228.
42. Lawford P, McKenzie D. Pressurized bronchodilator aerosol technique: influence of breath-holding time and relationship of inhaler to the mouth. Br J Dis Chest 1982;76:229-233.
43. Grainger JR. Correct use of aerosol inhalers. Can Med Assoc J 1977;116:584-585.
44. Woolf CR. Correct use of pressurized aerosol inhalers. Can Med Assoc J 1979;121:710-711.
45. Wilson AF, Mukai DS, Ahdout JJ. Effect of canister temperature on performance of metered dose inhalers. Am Rev Respir Dis 1991;143:1034-1037.
46. Morén F. Drug deposition of pressurized inhalation aerosols II. Influence of vapor pressure and metered volume. Int J Pharmacol 1985;1:213-218.
47. Heimer D, Shim C, Williams H. The effect of sequential inhalations of metaproterenol aerosol in asthma. J Allergy Clin Immunol 1980;66:75-77.
48. Pedersen S. The importance of a pause between the inhalation of two puffs of terbutaline from a pressurized aerosol with a tube spacer. J Allergy Clin Immunol 1986;77:505-509.
49. Epstein SW, Manning CPR, Ashley MJ, Corey PN. Survey of the clinical use of pressurized aerosol inhalers. Can Med Assoc J 1979;120:813-816.
50. Orehek J, Gayrard P, Grimand CH, Charpin J. Patient error in the use of bronchodilator metered aerosols. Br Med J 1976;1:76-77.
51. Shim C, Williams MH. The adequacy of inhalation of aerosol from canister nebulizers. Am J Med 1980;69: 891-896.
52. Paterson IC, Crompton GK. Use of pressurised aerosols by asthmatic patients. Br Med J 1976;1:76-77.
53. Earis J, Bernstein A. Misuse of pressurized nebulizers (letter). Br Med J 1978;1:1554-1555.
54. Coady T, Steward C, Davies H. Use of pressurized aerosols by asthmatic patients (letter). Br Med J 1973;3:833-834.
55. Roberts RJ, Robinson JD, Doering PL, Dallman JJ, Steeves RA. A comparison of various types of patient instruction in the proper administration of metered inhalers. Drug Intell Clin Pharm 1982;16:53-59.
56. O'Bey KA, Jim LK, Gee JP, Cowen ME, Quigley AE. An education program that improves the psychomotor skills needed for metaproterenol inhaler use. Drug Intell Clin Pharm 1982;16:945-948.
57. Self TH, Brooks JB, Lieberman P, Ryan MR. The value of demonstration and role of the pharmacist in teaching the correct use of pressurized bronchodilators. Can Med Assoc J 1983;128:129-131.
58. Allen SC, Prior A. What determines whether an elderly patient can use a metered dose inhaler correctly? Br J Dis Chest 1986;80:45-49.
59. Armitage JM, Williams SJ. Inhaler technique in the elderly. Age Ageing 1988;17:275-278.
60. Henney HR III, Blatt RS. Knowledge of nurses and respiratory therapists about using canister nebulizers. Am J Hosp Pharm 1984;41:2403-2405.
61. DeTullio PL, Corson ME. Effect of pharmacist counseling on ambulatory patients' use of aerosolized bronchodilators. Am J Hosp Pharm 1987;44:1802-1806.
62. Dolovich M, Ruffin R, Corr D, Newhouse MT. Clinical evaluation of a simple demand inhalation MDI aerosol delivery device. Chest 1983;84:36-41.
63. König P. Spacer devices used with metered-dose inhalers: Breakthrough or gimmick? Chest 1985;88:276-284.
64. Sackner MA, Kim CS. Recent advances in the management of obstructive airways disease: auxiliary MDI aerosol delivery systems. Chest 1985;88(2, Suppl): 161S-170S.
65. Kim CS, Eldridge MA, Sackner MA. Oropharyngeal deposition and delivery aspects of metered-dose inhaler aerosols. Am Rev Respir Dis 1987;135:157-164.
66. Corr D, Dolovich M, McCormack D, Ruffin R, Obminski G, Newhouse M. Design and characteristics of a portable breath actuated, particle size selective medical aerosol inhaler. J Aerosol Sci 1982;13:1-7.
67. Newman SP, Morén F, Pavia D, Little F, Clarke S. Deposition of pressurized suspension aerosols inhaled through extension devices. Am Rev Respir Dis 1981; 124:317-320.
68. Newman SP, Woodman G, Clarke SW, Sackner MA. Effect of InspirEase on the deposition of metered-dose aerosols in the human respiratory tract. Chest 1986; 89:551-556.
69. Gleeson JGA, Price JF. Nebuhaler technique. Br J Dis Chest 1988;82:172-174.
70. Niven RW, Haver K, Brain JD. An evaluation of the performance of several inhalation aerosol spacer devices using cascade impaction (abstract). J Aerosol Sci (in press) 1991.
71. Newman SP, Millar AB, Lennard-Jones TR, Morén F, Clarke S. Improvement of pressurised aerosol deposition with Nebuhaler spacer device. Thorax 1984;39: 935-941.
72. Fairshter RD. Evaluation of a metered-dose aerosol delivery system using a partial flow-volume curve. Am Rev Respir Dis 1987;135:741-743.

73. Crimi N, Palermo F, Cacopardo B, Vancheri C, Oliver R, Palermo B, et al. Bronchodilator effect of Aerochamber and InspirEase in comparison with metered dose inhaler. Eur J Respir Dis 1987;71:153-157.
74. Lee H, Evans HE. Evaluation of inhalation aids of metered dose inhalers in asthmatic children. Chest 1987; 91:366-369.
75. O'Reilly JF, Gould G, Kendrick AH, Laszlo G. Domiciliary comparison of terbutaline treatment by metered dose inhaler with and without conical spacer in severe and moderately severe chronic asthma. Thorax 1986;41: 766-770.
76. Fuller HD. Comparison of two chamber devices in patients using a metered-dose inhaler with satisfactory technique. Can Med Assoc J 1986;135:625-629.
77. Morris J, Milledge JS, Moszoro H, Higgins A. The efficacy of drug delivery by a pear-shaped spacer and metered dose inhaler. Br J Dis Chest 1984;78:383-387.
78. Pauwels R, Lamont H, Hidinger K, Van der Straeten M. Influence of an extension tube on the bronchodilator efficacy of terbutaline delivered from a metered dose inhaler. Respiration 1984;45:61-66.
79. Epstein SW, Parsons JE, Corey PN, Worsby GH, Reilly PA. A comparison of three means of pressurized aerosol inhaler use. Am Rev Respir Dis 1983;128:253-255.
80. Fuglsang G, Pedersen S. Cumulative dose response relationship of terbutaline delivered by three different inhalers. Allergy 1988;43:348-352.
81. Tobin MJ, Jenouri G, Danta J, Kim C, Watson H, Sackner MA. Response to bronchodilator drug administration by a new reservoir aerosol delivery system and a review of other auxillary delivery systems. Am Rev Respir Dis 1982;126:670-675.
82. Salzman GA, Steele MT, Pribble JP, Elenbaas RM, Pyszczynski DR. Aerosolized metaproterenol in the treatment of asthmatics with severe airflow obstruction. Chest 1989;95:1017-1020.
83. Jasper AC, Mohsenifar Z, Kahan S, Goldberg HS, Koerner SK. Cost-benefit comparison of aerosol bronchodilator delivery methods in hospitalized patients. Chest 1987;91:614-618.
84. Summer W, Elston R, Tharpe L, Nelson S, Haponik EF. Aerosol bronchodilator delivery methods: relative impact on pulmonary function and cost of respiratory care. Arch Intern Med 1989;149:618-623.
85. Berry RB, Shinto RA, Wong FH, Despars JA, Light RW. Nebulizer vs spacer for bronchodilator delivery in patients hospitalized for acute exacerbations of COPD. Chest 1989;96:1241-1246.
86. Turner JR, Corkery KJ, Eckman D, Gelb AM, Lipavsky A, Sheppard D. Equivalence of continuous flow nebulizer and metered-dose inhaler with reservoir bag for treatment of acute airflow obstruction. Chest 1988;93: 476-481.
87. Green AB, Jackson CL. Terbutaline metered-dose inhalation vs metaproterenol by hand-held nebulization: a comparison in black inner-city COPD patients. J Natl Med Assoc 1988;80:393-396.
88. Gervais A, Bégin P. Bronchodilatation with a metered-dose inhaler plus an extension, using tidal breathing vs jet nebulization. Chest 1987;92:822-824.
89. Berenberg MJ, Cupples LA, Baigelman W, Pearce L. Comparison of metered dose inhaler attached to an Aerochamber with an updraft nebulizer for the administration of metaproterenol in hospitalized patients. J Asthma 1985;22:87-92.
90. Pedersen JZ, Bundgaard A. Comparative efficacy of different methods of nebulising terbutaline. Eur J Clin Pharmacol 1983;25:739-742.
91. Cushley MJ, Lewis RA, Tattersfield AE. Comparison of three techniques of inhalation on the airway response to terbutaline. Thorax 1983;38:908-913.
92. Hess D. How should bronchodilators be administered to patients being mechanically ventilated? Respir Care 1991;36:377-394.
93. Weber RW, Petty WE, Nelson HS. Aerosolized terbutaline in asthmatics. J Allergy Clin Immunol 1979; 63:116-121.
94. Dolovich MG, Killian D, Wolff RK. Pulmonary aerosol deposition in chronic bronchitis: intermittent positive pressure breathing versus quiet breathing. Am Rev Respir Dis 1977;115:397-402.
95. Smelzer TH, Barnett TB. Bronchodilator aerosol: comparison of administration methods. JAMA 1973;223: 884-889.
96. Moore RB, Cotton EK, Pinney MA. The effect of intermittent positive-pressure breathing on airway resistance in normal and asthmatic children. J Allergy Clin Immunol 1972;49:137-142.
97. The IPPB Trial Group. Intermittent positive pressure breathing therapy of chronic obstructive pulmonary disease. Ann Intern Med 1983;99:612-620.
98. Petty TL. A critical look at IPPB (editorial). Chest 1974;66:1.
99. Gold MI. The present status of IPPB therapy. Chest 1975;67:469-472.
100. Chang N, Levison H. The effect of a nebulized bronchodilator administered with or without intermittent positive pressure breathing on ventilatory function in children with cystic fibrosis and asthma. Am Rev Respir Dis 1972;106:867-872.
101. Cayton RM, Webber B, Paterson JW, Clark LJH. A comparison of salbutamol given by pressure-packed aerosol or nebulization via IPPB in acute asthma. Br J Dis Chest 1978;72:222-224.
102. Choo-Kang YFJ, Grant IWB. Comparison of two methods of administering bronchodilator aerosol to asthmatic patients. Br Med J 1975;2:119-125.
103. Nizami NP, Vakil DV, Lozynsky A, Nizami RM. Automatic piercing Spinhaler (Halermatic): a comparative study. Ann Allergy 1988;60:399-402.
104. Crompton GK. Clinical use of dry powder systems. Eur J Respir Dis (Suppl) 1982;122:96-99.
105. Hansen NCG. Terbutaline as powder inhalation from Bricanyl Turbuhaler compared to terbutaline as neb-

ulizer solution in severe chronic airways obstruction. Eur Respir J 1989;2(Suppl):716-720.
106. Balmes JR. Propellant gases in metered dose inhalers: their impact on the global environment. Respir Care 1991;36:1037-1044.
107. Pedersen S. How to use a Rotahaler. Arch Dis Child 1986;61:11-14.
108. Auty RM, Brown K, Neale MG, Snashall PD. Respiratory tract deposition of sodium cromoglycate is highly dependent upon technique of inhalation using the Spinhaler. Br J Dis Chest 1987;81:371-380.
109. Newman SP. Delivery of therapeutic aerosols. Probs Respir Care 1988;1:53-82.
110. Tukiainen H, Terho EO. Comparison of inhaled salbutamol powder and aerosol in asthmatic patients with low peak expiratory flow level. Eur J Clin Pharmacol 1985;27:645-647.
111. Assoufi BK, Hodson ME. High dose salbutamol in chronic airflow obstruction: comparison of nebulizer with Rotacaps. Respir Med 1989;83:415-420.
112. Grimwood K, Johnson-Barrett JJ, Taylor B. Salbutamol: tablets, inhalational powder, or nebuliser? Br Med J 1981;282:105-106.
113. Johnsen CR, Weeke ER. Turbuhaler: a new device for dry powder terbutaline inhalation. Allergy 1988;43:392-395.
114. Pover GM, Langdon CG, Jones SR, Fidler C. Evaluation of a breath operated powder inhaler. J Int Med Res 1988;16:201-203.
115. Bronsky E, Bucholtz GA, Busse WW, Chervinsky P, Condemi J, Ghafouri MA, et al. Comparison of inhaled albuterol powder and aerosol in asthma. J Allergy Clin Immunol 1987;79:741-747.
116. Persson G, Gruvstad E, Stahl E. A new multiple dose powder inhaler (Turbuhaler), compared with a pressurized inhaler in a study of terbutaline in asthmatics. Eur Respir J 1988;1:681-684.
117. Swinburn PD, Sexton M. Inhaled bronchodilators: a comparison of different methods of inhaling. NZ Med J 1981;18:340.
118. Sovijarvi ARA, Lahdensue A, Muittari A. Bronchodilating effect of salbutamol inhalation powder and salbutamol aerosol after methacholine-induced bronchoconstriction. Curr Ther Res 1982;32:566-573.
119. Edmunds AT, McKenzie S, Tooley M, Godfrey S. A clinical comparison of beclomethasone dipropionate delivered by pressurized aerosol and as a powder from a Rotahaler. Arch Dis Child 1979;54:233-235.
120. Muittari A, Ahonen A. Comparison of the bronchodilator effect of inhaled salbutamol powder and pressurized salbutamol aerosol. Curr Ther Res 1979;25:804-808.
121. Smith JM, Gwynn CM. A clinical comparison of aerosol and powder administration of beclomethasone dipropionate in asthma. Clin Allergy 1978;8:479-481.
122. Jenkins SC, Moxham J. High dose salbutamol in chronic bronchitis: comparison of 400 mcg, 1 mg, 1.6 mg, 2 mg and placebo delivered by Rotahaler. Br J Dis Chest 1987;81:242-247.
123. Corris PA, Neville E, Nariman S, Gibson GJ. Dose-response study of inhaled salbutamol powder in chronic airflow obstruction. Thorax 1983;38:292-296.
124. Vathenen AS, Britton JR, Ebden P, Cookson JB, Wharrad HJ, Tattersfield AE. High-dose inhaled albuterol in severe chronic airflow limitation. Am Rev Respir Dis 1988;138:850-855.
125. Persson G, Wirjen JE. The bronchodilator response from increasing doses of terbutaline inhaled from a multi-dose powder inhaler (Turbuhaler). Eur Respir J 1990;3:24-26.
126. McFadden ER, Mills R. Inhaled albuterol powder for the prevention of exercise-induced bronchospasm. Immun Allergy Prac 1986;8:199-203.
127. Horne D. Nebulizer for anesthetic system. Anesthesiology 1962;23:583-584.
128. Small GA. Aerosolization of drugs during inhalation anesthesia. Anesthesiology 1964;25:239.
129. MacIntyre NR, Silver RM, Miller CW, Schuler F, Coleman RE. Aerosol delivery in intubated, mechanically ventilated patients. Crit Care Med 1985;13:81-85.
130. Ahrens RC, Ries RA, Popendorf W, Wiese JA. The delivery of therapeutic aerosols through endotracheal tubes. Pediatr Pulmonol 1986;2:19-26.
131. Cameron D, Clay M, Silverman M. Evaluation of nebulizers for use in neonatal ventilator circuits. Crit Care Med 1990;18:866-870.
132. Henry WD, Chatburn RL. Effects of manual versus mechanical ventilation on aerosol dose efficiency (abstract). Respir Care 1988;33:914.
133. Fraser I, DuVall A, Dolovich M, Newhouse MT. Therapeutic aerosol delivery in ventilator systems (abstract). Am Rev Respir Dis 1981;123:107.
134. Flavin M, MacDonald M, Dolovich M, Coates G, O'Brodovich H. Aerosol delivery to the rabbit lung with an infant ventilator. Pediatr Pulmonol 1986;2:35-39.
135. Cameron D, Arnot R, Clay M, Silverman M. Aerosol delivery in neonatal ventilator circuits: a rabbit lung model. Pediatr Pulmonol 1991;10:208-213.
136. Dählback M, Wollmer P, Drefeldt B, Jonson B. Controlled aerosol delivery during mechanical ventilation. J Aerosol Med 1989;2:339-347.
137. Gay PG, Rodarte JR, Tayyab H, Hubmayr RD. Evaluation of bronchodilator responsiveness in mechanically ventilated patients. Am Rev Respir Dis 1987;136:880-885.
138. Brudno DS, Parker DH, Slaton G. Response of pulmonary mechanics to terbutaline in patients with bronchopulmonary dysplasia. Am J Med Sci 1989;297:166-168.
139. Wilkie RA, Bryan MH. Effect of bronchodilators on airway resistance in ventilator-dependent neonates with chronic lung disease. J Pediatr 1987;111:278-282.
140. Beaty CD, Ritz RH, Benson MS. Continuous in-line nebulizers complicate pressure support ventilation. Chest 1989;96:1360-1363.

141. Koss JA, Connie TA, Eitzer HE, LoSasso AM. Bacterial contamination potential of sterile, prefilled humidifiers and nebulizer reservoirs. Heart Lung 1979;8:1117-1121.
142. Bridenbaugh PO. An endotracheal spray for the relief of bronchospasm. Anesthesiology 1966;27:860.
143. Gold MI. A convenient and accurate nebulizer. Anesthesiology 1967;28:1102-1104.
144. Fresoli RP, Smith RM, Young JA, Gottshall SC. Use of aerosol isoproterenol in an anesthesia circuit. Anesth Analg 1968;47:127-132.
145. Gold MI. Treatment of bronchospasm during anesthesia. Anesth Analg 1975;54:783-786.
146. Sprague DH. Treatment of intraoperative bronchospasm with nebulized isoetharine. Anesthesiology 1977;46: 222-224.
147. Duckett JE. A simple device for delivering bronchodilators into the anesthesia circuit. Anesthesiology 1985;62:699-710.
148. Diamond MJ. Delivering bronchodilators into the anesthesia circuit (letter). Anesthesiology 1986;64:531.
149. Bush GL. Aerosol delivery devices for the anesthesia circuit (letter). Anesthesiology 1986;65:240.
150. Newell R, Shulman MS. The administration of bronchodilators into the anesthesia circuit. Anesthesiology 1987;66:716-717.
151. Gold MI, Marcial E. An anesthetic adapter for all metered dose inhalers. Anesthesiology 1988;68:964-966.
152. Hess D, Beener C, Kacer Watson K. An evaluation of the effectiveness of metered dose inhaler (MDI) use with mechanical ventilation (abstract). Respir Care 1988;33:910,914.
153. Crogan SJ, Bishop MJ. Delivery efficiency of metered dose aerosols given via endotracheal tubes. Anesthesiology 1989;70:1008-1010.
154. Fuller HD, Dolovich MB, Posmituck G, Wong Pack W, Newhouse MT. Pressurized aerosol versus jet aerosol delivery to mechanically ventilated patients: comparison of dose to the lung. Am Rev Respir Dis 1990;141:440-444.
155. Fuller H, Dolovich M, Turpie F, Posmituck G, Wong Pack W, Newhouse MT. Aerosol deposition to the lungs by MDI in ventilated patients: ET tubes vs tracheostomy (abstract). Chest 1990;98(Suppl):27S.
156. Gay PC, Patel HG, Nelson SB, Gilles B, Hubmayr RD. Metered dose inhalers for bronchodilator delivery in intubated, mechanically ventilated patients. Chest 1991; 99:66-71.
157. Hess D, Fillman D, Daugherty A, Rexrode WO, Smoker JM, Rhoads JE. Use of metered dose inhalers in intubated patients (abstract). Respir Care 1989;34:1027.
158. Gutierrez CJ, Nelson R. Short-term bronchodilation in mechanically ventilated patients receiving metaproterenol via SVN and MDI (abstract). Respir Care 1988;33:910.
159. Fernandez A, Lazaro A, Garcia A, Aragon C, Cerda E. Bronchodilators in patients with chronic obstructive pulmonary disease on mechanical ventilation. Am Rev Respir Dis 1990;141:164-168.
160. Bishop MJ, Larson RP, Buschman DL. Metered dose inhaler aerosol characteristics are affected by the endotracheal tube actuator/adapter used. Anesthesiology 1990;73:1263-1265.
161. Taylor RH, Lerman J. High efficiency delivery of salbutamol with a metered-dose inhaler in narrow tracheal tubes and catheters. Anesthesiology 1991;74:360-363.
162. Peterfreund RA. A simple catheter extension improves delivery efficiency of metered dose inhalers: a quantitative evaluation (abstract). Anesthesiology 1990;72: A486.
163. Hess D. The delivery of aerosolized bronchodilator to mechanically ventilated intubated adult patients (editorial). Respir Care 1990;35:399-404.

Dosing Strategies for Bronchodilator Aerosol Delivery

Donald P Tashkin MD

Introduction

Many pharmacologic agents are delivered in the form of therapeutic aerosols to the lower airways, including bronchodilators, anti-inflammatory compounds (corticosteroids, cromolyn sodium), mucolytic agents, and selective antagonists of chemicals that mediate asthma (administered for diagnostic and experimental purposes). In this paper I focus specifically on dosing strategies for delivery of aerosolized bronchodilators to the lower respiratory tract. Of the three major classes of bronchodilators in current use (beta-adrenergic agonists, anticholinergic compounds, and methylxanthines), only beta-adrenergic agonists and anticholinergics can be effectively administered as aerosols; aerosolized theophylline is commonly known to cause airway irritation and only marginal bronchodilation. Consequently, I will confine my attention to the selection of optimal dosing regimens for beta-adrenergic and anticholinergic bronchodilators.

Determinants of Dose Requirements for a Beta-Adrenergic Agonist

The dose of a beta-adrenergic aerosol that will produce optimal bronchodilation with minimal adverse effects is determined by several factors, including: (1) the type of beta-adrenergic agonist, (2) the method of aerosol delivery, and (3) the response characteristics of the patient.

Type of Beta-Adrenergic Agonist

The recommended dose of a specific type of beta-adrenergic agonist is determined by its bronchodilator potency as reflected by its in-vitro and in-vivo dose-response characteristics. These are conveniently expressed by the ED_{50} (ie, the dose of a beta-adrenergic agonist required to produce 50% maximal relaxation of pharmacologically or electrically contracted tracheobronchial smooth muscle). Of the beta-adrenergic agonists in current use in the U.S., the order of potency is: isoproterenol > albuterol > terbutaline > isoetharine > bitolterol > metaproterenol.[1] Fenoterol, which is not approved for use in the U.S., is slightly more potent than albuterol. In general, the dose delivered with each actuation of a commercially available beta-adrenergic-agonist metered dose inhaler (MDI) has been selected by the manufacturer to be bioequivalent in potency to that of other beta-adrenergic-agonist MDIs. A notable exception to this rule is the fenoterol MDI, which is designed to deliver approximately twice the bioequivalent dose per actuation of that delivered by other beta-adrenergic-agonist MDIs.

Method of Aerosol Delivery

The dose of beta-adrenergic-agonist aerosol required to produce a desired degree of bronchodilation is determined by the dose that is actually delivered to the beta adrenoreceptors of bronchial smooth muscle. This delivered dose is influenced by the method used for aerosol delivery. Factors

Dr Tashkin is Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Department of Medicine, UCLA School of Medicine, Los Angeles, California.

A version of this paper was presented by Dr Tashkin during the Consensus Conference on Aerosol Delivery, sponsored by the American Association for Respiratory Care, the American Respiratory Care Foundation, and the journal RESPIRATORY CARE, January 10-12, 1991, in Cancun, Mexico.

Reprints: Donald P Tashkin MD, Department of Medicine, UCLA School of Medicine, Los Angeles CA 90024.

that affect drug delivery to the lower respiratory tract include

- the type of aerosol delivery device—small-volume jet nebulizer (SVJN), ultrasonic nebulizer (USN), MDI with or without an extension device (or spacer), or dry powder inhaler;
- the output characteristics of the aerosol delivery device—the number and size of drug-containing particles, particle size distribution, and hygroscopicity of particles;
- the method used to operate the aerosol-generating device—nebulizer 'fill' volume, driving pressure, continuous versus intermittent nebulization, duration of nebulization, periodic 'tapping' of the nebulizer when using an SVJN or shaking and inversion of the canister and proper actuation-inspiration coordination when using an MDI without a spacer;
- the patient's inhalation pattern—inspiratory flowrate, tidal volume, end-inspiratory breath-hold duration; and
- the type of airway interface—mouthpiece, mask, endotracheal tube (ETT), or tracheostomy tube.

Patient-Response Characteristics

The response of a patient to a given dose of bronchodilator depends on a number of host factors, which have previously been reviewed,[2] including:

- the underlying responsiveness of the patient's airways, which, in turn, is influenced by the type of disease (eg, asthma vs irreversible, chronic obstructive pulmonary disease [COPD]), the degree of inflammation, and the thickness of the airway wall;[3]
- the baseline degree of airflow obstruction;
- the stability of the obstructive disease (chronic versus acute exacerbation);
- the presence and degree of tachyphylaxis; and
- residual effects of previously or concomitantly administered bronchodilators.

The measured response to a bronchodilator can also be influenced by the specific tests used to measure that response. For example, tests of forced exhalation can be confounded by constrictor effects of a single deep breath[4] and by dynamic airway compression.[5] Improvement in severe acute asthma is sometimes more apparent from measurements of lung volume (ie, when reductions in the degree of hyperinflation are observed) than from measurements of airway caliber.[6]

The perceived effectiveness of a bronchodilator can vary depending on the method used to express the bronchodilator response.[7] For example, when the baseline degree of airflow obstruction is severe, a small absolute improvement in airway caliber may be magnified by reporting it as a large percent improvement over baseline. Expressing improvement as either percent of maximal achievable improvement or as percent of the predicted value may help to better convey the true effectiveness of a bronchodilator, but problems in accurate interpretation may still exist.

Conclusions regarding bronchodilator efficacy may also be influenced by the specific response variable evaluated. For example, two different doses of a beta-adrenergic agonist may cause the same peak magnitude of bronchodilation, but the duration of bronchodilation may be shorter following the lower of the two doses. Furthermore, the duration of the protective effect of a beta-adrenergic agonist against experimentally induced (and, presumably, naturally occurring) bronchoconstriction is considerably shorter than the duration of its bronchodilator effect.[8] This dichotomy in the duration of relaxation of spontaneously contracted airway smooth muscle (bronchodilation) versus inhibition of induced bronchoconstriction (protection) is probably due largely to functional antagonism. Under baseline conditions of spontaneous bronchial narrowing, constrictor influences are less than those produced by inhalation challenge with large doses of constrictor agonists. The more potent the constrictor influences, the higher the dose of a beta-adrenergic agonist required to counteract these influences (functional antagonism). In other words, in the face of increased bronchoconstriction (as occurs in acute severe asthma or with the experimental administration of high doses of a constrictor agonist), the bronchodilator potency of beta-adrenergic agonists is reduced, as reflected by a rightward shift in the bronchodilator dose-response curve and an increase in the ED_{50} (Fig. 1).[9,10] As a result, higher doses of beta-adrenergic

agonists are required for the treatment of acute severe asthma than for the treatment of stable chronic asthma. Furthermore, for a given rate of degradation of a beta-adrenergic agonist, concentration of the beta agonist becomes suboptimal sooner when higher doses are required to counteract potent constrictor effects, as in acute severe asthma. Consequently, more frequent doses of a bronchodilator are required under these conditions.

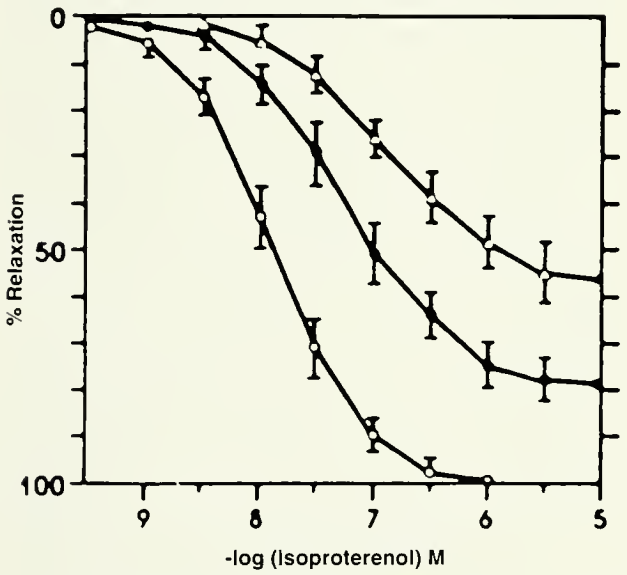


Fig. 1. Cumulative dose-response curves for isoproterenol-induced relaxation of guinea pig trachea contracted with increasing concentrations of methacholine (Mch). ○ = 0.3 μmol Mch; ● = 1.0 μmol Mch; △ = 3.0 μmol Mch. These curves illustrate marked functional antagonism between the beta-adrenergic agonist (isoproterenol) and the contractile agent (Mch). (Reprinted, with permission, from Reference 10.)

Standard vs Optimal Doses of a Beta-Adrenergic Agonist

Because of the many variables that influence the dose requirements of a beta-adrenergic bronchodilator, it is clear that no 'standard' dose is applicable to all patients under all conditions. The doses and frequency of dosing recommended by the manufacturers (Table 1) for beta-adrenergic agonists delivered by an MDI are largely based on studies of chronic stable asthmatics participating in FDA-approved clinical trials. These dosage regimens often do not suffice for the treatment of severe acute asthma for at least two reasons: (1) Acute severe asthma is associated with greater functional antagonism than is chronic stable asthma and, therefore, requires larger and more frequent doses. (2) The widespread airway narrowing characteristic of acute severe asthma (due to worsening bronchospasm, inflammatory edema, and mucus secretion) further impairs delivery of a given dose of beta-adrenergic-agonist aerosol to beta-receptor sites in the lung periphery, with excessive deposition in the narrowed central airways.

Despite the greater dosage requirements for severe asthma, many physicians are reluctant to sanction the administration of doses in excess of those recommended by the manufacturers or at intervals shorter than every 4 hours. This reluctance may partially be attributed to the "epidemic" of asthma deaths reported in the United Kingdom and other countries during the 1960s. Initially, this epidemic was attributed to the toxicity of high doses of MDI-administered beta-adrenergic agonists;[11] however, subsequent analysis has led to the conclusion that the excess asthma mortality may have been the result of excessive reliance on beta-

Table 1. Manufacturers' Dosing Recommendations for MDIs*

Product	Dose/ Actuation	Recommended Dose (Adults)
Isoproterenol (Medihaler-Iso)	80 μg	1-2 sprays every 2-4 h as needed
Isoetharine (Bronkometer)	340 μg	1-2 puffs every 4-6 h, may increase to every 1-2 h for acute attacks
Metaproterenol	650 μg	2-3 puffs every 4-6 h
Albuterol	90 μg	1-2 puffs every 4-6 h
Terbutaline	200 μg	1-2 puffs every 4-6 h
Bitolterol	370 μg	1-3 puffs every 4-6 h
Fenoterol	160 μg	1-2 puffs every 4-6 h

*Based on package inserts reproduced in 1990 Physician's Desk Reference.

adrenergic-agonist therapy (ie, undertreatment with alternative, nonbronchodilator antiasthma agents such as steroids rather than overtreatment with beta-adrenergic agonists and consequent cardiovascular toxicity).[12]

Despite the pervasiveness of concerns regarding toxicity of MDI-delivered beta-adrenergic agonists in high doses, the maximum doses recommended by the manufacturers for beta-adrenergic agonists administered in solution form (as 'wet' aerosols by SVJN) are at least 10 times higher than those recommended for identical agents adminstered by MDI (Table 2). The basis for the disparity in these dosage recommendations is not clear, but probably reflects the recognition that delivery of beta-adrenergic agonists by SVJN is less efficient than delivery by MDI. Indeed, some studies show a tenfold rightward shift in the dose-response curve for a solution aerosol compared to an MDI aerosol (Fig. 2).[13] Interestingly, although most studies demonstrate that SVJNs are less efficient than MDIs in delivering beta-adrenergic agonists to the lower airway, the variability in the efficiency ratios of SVJNs to MDIs is wide,[14] ranging from 1:2 to 1:12.5. This variable efficiency probably reflects the variability in types of SVJNs, in output characteristics of SVJNs, in methods used to operate SVJNs, in patient inhalation patterns, in techniques of MDI administration, and in the use or non-use of MDI-spacer devices. It is clear that bronchodilator response is not determined simply by the dose of the drug added to the nebulizer or by the particular aerosol-generating device used, but rather by the actual dose of beta-adrenergic agonist reaching the lower respiratory tract.

Table 2. Manufacturers' Dosing Recommendations for Solution Aerosols*

Product	Concentration	Recommended Dose (Adults)
Isoproterenol HCl	0.5% (1:200) 5 mg/mL	0.25 mL (1.25 mg) via compressor-driven nebulizer
Isoetharine	0.25%, 0.5%, and 1%	0.5 mL of 1% solution diluted 1:3 with 0.9% saline
Metaproterenol	5%, 0.6% unit dose vial (2.5 mL)	0.3 mL (15 mg) of 5% solution diluted in 2.5 mL 0.9% saline every 2-4 h
Albuterol	0.5%, 0.083% unit dose vial (3 mL)	2.5 mg diluted in 3 mL normal saline 3 to 4 times daily
Terbutaline	0.1% (1 mg/mL)	5-7 mg (5-7 mL) undiluted every 4-6 h as needed (not approved)

*Based on package inserts reproduced in 1990 Physician's Desk Reference.

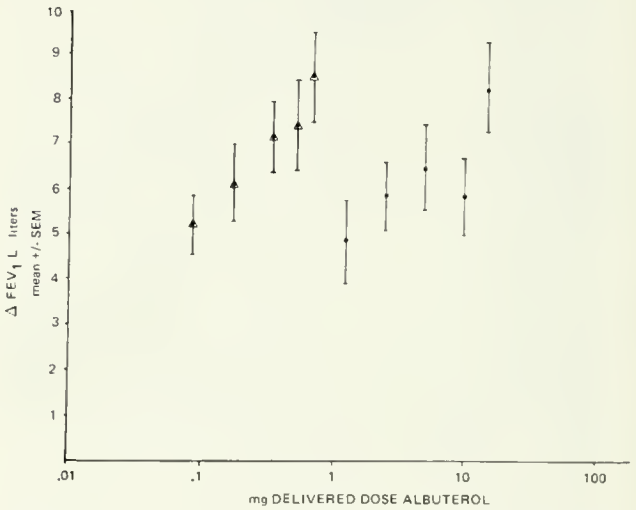


Fig. 2. Dose-response curves for FEV_1 versus aerosolized isoproterenol delivered by MDI △ (26 patients with asthma) and by IPPB ● (18 patients with asthma). Note the approximately tenfold rightward shift in the dose-response curve for IPPB- versus MDI-delivered isoproterenol. (Reprinted, with permission, from Reference 13.)

Rather than being constrained by manufacturers' recommended standard and maximum doses and dose frequencies, the physician should select the optimal dose and dose interval for a given individual. This optimal dosing regimen varies between delivery devices, within delivery devices depending on the method of use, between patients, and within patients depending on changes in pulmonary status. Findings from recent studies provide reasonable guidelines for determining optimal dosing regimens for patients with moderate-to-severe chronic asthma or COPD and severe acute asthma.

Moderate-to-Severe Chronic Asthma

Mestitz et al[15] studied 9 patients with moderate-to-severe chronic airflow limitation due to asthma (FEV_1 < 2.2 L; FEV_1/VC ratio < 54%) receiving regular beta-adrenergic-agonist therapy in standard doses by either MDI or nebulizer. On separate days, cumulative-dose-FEV_1 response curves were constructed for terbutaline administered by either MDI or nebulizer. The mean dose required to produce maximal bronchodilation was 2.8 mg for the MDI (5 times the usual recommended MDI dose) and 5.8 mg for the nebulizer (approximately 2 times the MDI dose). Patients were then treated for 2 weeks with either 1.25 mg terbutaline by MDI (2.5 times the usual dose) or the bioequivalent dose (2.5 mg) by nebulizer 4 times each day for 2 weeks, before crossing over in random, double-blind fashion to the alternative form of aerosol therapy for an additional 2 weeks. Response was assessed by measurement of FEV_1, VC, exercise tolerance (6-min walk), symptoms, and extra beta-adrenergic-agonist use. The increased dosages resulted in significant improvement in VC and exercise performance compared with standard dosages, without any demonstrable side effects. The MDI and nebulizer yielded comparable results.

Prior and co-workers[16] studied 8 patients with chronic severe asthma (mean FEV_1 0.831 L), who had been poorly controlled by conventional doses of the inhaled beta-adrenergic agonist albuterol (200-400 μg 4 times each day) despite concomitant treatment with inhaled and/or oral corticosteroids. After cumulative dose-response curves demonstrated that a mean dose of 4 mg terbutaline was required to produce maximal bronchodilation, these patients were treated over two 2-week periods with high-dose inhaled terbutaline (4 mg, 4 times each day, or 8 times the recommended dose) via either an MDI (delivering 1 mg/actuation) with tube spacer or a power nebulizer, in randomized crossover fashion. All patients improved both objectively (daily peak flow measurements) and subjectively with the high-dose regimen, and no patient reported any side effects. No differences were noted between the nebulizer or MDI-spacer delivery systems.

The results of these two small-scale studies[15,16] suggest that chronic asthmatics with moderate-to-severe airflow obstruction may benefit from maintenance doses 2.5-8 times higher than conventional doses of aerosolized beta-adrenergic agonists, without experiencing significant side effects. These findings also support the results of several other studies that indicate comparable efficacy of MDI and wet nebulizer when bio-equivalent doses are administered. On the other hand, recent data[17] suggest that in chronic asthmatics who are treated with inhaled and/or oral corticosteroids, additional maintenance therapy with regularly scheduled doses of inhaled beta-adrenergic agonists can lead to worsening of asthma symptoms (especially at night) and lowering of morning peak-flowrates, compared to 'as-needed' (PRN) use of beta-adrenergic-agonist aerosols. The reasons for these findings are unclear, but may reflect an adverse effect of chronic beta-adrenergic-agonist therapy on airway reactivity[18] and/or on mucus.[17]

Acute Severe Asthma

Benton and colleagues[19] evaluated an individualized dose-titration regimen for treating children presenting to the emergency room with acute exacerbations of asthma. This regimen consisted of an initial 2 actuations of an albuterol MDI with a spacer attachment (Aerochamber, Monaghan Medical, Plattsburgh NY) followed by peak expiratory flow (PEF) measurements and auscultation. Additional albuterol (1-2 actuations) was administered every 1-2 minutes followed by objective assessment of response until maximal improvement was achieved or a ceiling dose of 20 actuations was reached. In the 13 patients studied, a mean (SD) dose of 8 (3) puffs (range, 4-14) was required, at an interval of 2 (2) minutes between successive puffs. The average overall percent improvement in PEF was 87% after the total mean dose of 8 actuations (23 μg/kg), as opposed to only 34% improvement over baseline after the conventional dose of 2 actuations; no adverse side effects were noted. In comparison, a retrospective analysis by the same authors[19] of the results of wet-nebulizer treatment of 25 patients presenting to the emergency room with acute asthma revealed only

a 40% improvement in PEF despite administration of a greater than fourfold-larger average dose of albuterol. These data support the efficacy and safety of individualized dose-titration of aerosolized beta-adrenergic agonists delivered by an MDI-spacer assembly up to as much as 7 times the conventional dose for the treatment of acute severe asthma in children.

A dosage interval of 3-4 hours between successive treatments of the longer-acting bronchodilator aerosols (eg, albuterol, terbutaline) is commonly recommended; however, in acute severe asthma, marked bronchoconstriction is usually associated with only a short duration of response to a bronchodilator. Therefore, in the treatment of acute severe asthma, the usual practice is to reduce the commonly recommended dosage interval for albuterol or terbutaline to 1 or 2 hours when necessary. Kelly et al[20] reviewed 44 pediatric ICU admissions for acute severe asthma in 27 children to assess the safety of nebulized terbutaline administered at frequent intervals over a prolonged period. The average dose per treatment was 0.2 mg/kg (range, 0.1-0.4 mg/kg). Within successive 6-hour periods over the first 36 hours of hospitalization, the mean interval between consecutive treatments ranged from 2.4-3.8 hours; the absolute interval between treatments during the first 24 hours ranged from 0.5-6 hours, and during the next 12 hours ranged from 2-6 hours. Despite such frequent administration of high doses of beta-adrenergic-agonist aerosols, heart rate progressively fell over the course of the 36 hours in conjunction with progressive improvement in respiratory status (evident by a parallel decline in respiratory rate). Interestingly, heart rate fell to a greater extent in those patients receiving higher ($\geq$ 0.2 mg/kg) than lower ($<$ 0.2 mg/kg) doses of terbutaline. These data support the safety of frequent administration of high doses of nebulized terbutaline over a prolonged period in the treatment of acute severe childhood asthma.

In the treatment of severe acute pediatric asthma Robertson et al[21] observed that asthma improved initially in some patients, but worsened before the next dose, even when dosage intervals were as short as 1-2 hours. After an initial nebulized dose of 0.15 mg/kg albuterol (maximum dose 5 mg), the efficacy of this same dose administered at hourly intervals was compared to the efficacy of divided doses of albuterol (0.05 mg/kg, maximum dose 1.7 mg) administered every 20 minutes for a total of 2.5 hours. The results show a smooth, progressive improvement in FEV_1 in the group treated at 20-minute intervals, in contrast to deterioration prior to the next scheduled dose as well as a diminished overall response in the group treated at hourly intervals (Fig. 3). The authors suggested that because the duration of bronchodilator response in severe acute asthma is frequently very short, airflow obstruction is more likely to worsen before the next scheduled nebulizer treatment in the hourly regimen than it is in the thrice-hourly regimen. The response to the hourly treatments is likely to be less because of poorer peripheral penetration of the aerosolized medication through airways that have been permitted to narrow between treatments.

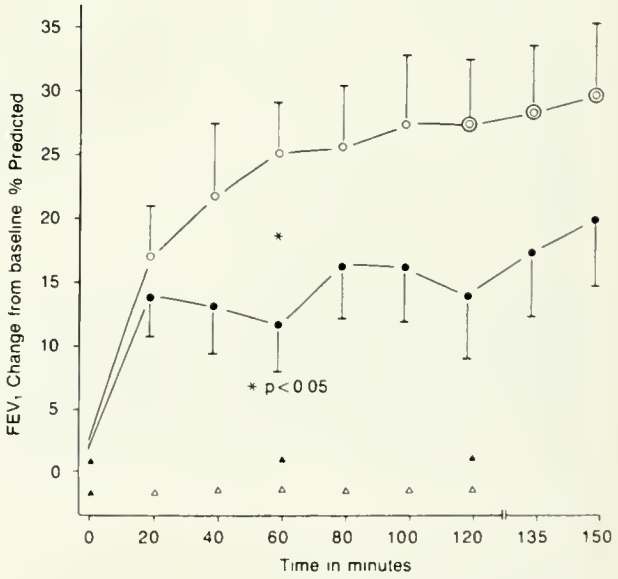


Fig. 3. Change in % predicted FEV_1 from baseline at 20-minute intervals in pediatric patients with acute severe asthma receiving nebulized albuterol (○ = 0.05 mg/kg every 20 minutes; ● = 0.15 mg/kg every hour). (Reprinted, with permission, from Reference 21.)

These findings suggest that small frequent doses of an aerosolized beta-adrenergic agonist have a greater overall therapeutic effect in acute severe asthma than do larger, less-frequent doses. These findings also support the practice of progressively

increasing the frequency of bronchodilator aerosol therapy in patients with acute severe asthma who are not responding to treatment at less-frequent intervals. If carried to the extreme, this practice could ultimately lead to continuous nebulization therapy (CNT). Continuous nebulization of $beta_2$-selective adrenergic agonists has been used in the management of severe acute asthma not responding to intermittent nebulization.[20,22] This approach to the treatment of status asthmaticus is viewed as being safer than constant intravenous infusion of the nonselective beta-adrenergic agonist isoproterenol, which has been associated with CPK-MB isoenzyme elevations, cardiac arrhythmias, myocardial ischemia, and both fatal and nonfatal myocardial infarction.[23-27] Moreover, nebulization therapy has been found to be as efficacious in the management of acute severe asthma as intravenous infusion of $beta_2$-selective adrenergic agonists,[28,29] which have greater potential than inhaled agents for systemic (especially cardiovascular) toxicity.[30]

Moler and co-workers[30] have described an approach to the management of acute severe childhood asthma consisting of methylprednisolone, aminophylline, and intermittently nebulized terbutaline, followed by CNT if necessary. These authors initially administered nebulized terbutaline in a dose of 2 mg every hour. If a favorable clinical response was not achieved, the same dose was administered 4 times at 30-minute intervals, followed by CNT if necessary. They reported providing CNT to 19 children during 27 episodes of severe asthma. The apparatus shown in Figure 4 was used to administer terbutaline in a dose of 4 mg/hour (0.4 mg/mL) per hour. The mean duration of CNT was 15.4 hours (range 3-37 hour). Asthma symptoms improved in all patients, elevated arterial P_{CO_2} levels declined, and no adverse effects were noted. The authors estimated that the highest bioavailable (systemically absorbed) dose from CNT of terbutaline administered to a 15-kg child at a rate of 4 mg/hour (or 4.44 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was 0.58 $\mu g \cdot kg^{-1} \cdot min^{-1}$, assuming 12% delivery to the lung and 1% to the mouth, and 100% absorption from the lung and buccal mucosa. The authors point out that this maximum estimated bioavailable dose from CNT is comparable to the maximum intravenous tocolytic dose (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) that can be used in pregnant women without observable adverse effects to the mother or fetus. These results support the effectiveness and safety of CNT in children with acute severe asthma, some of whom might otherwise require treatment with intravenous isoproterenol or mechanical ventilation.

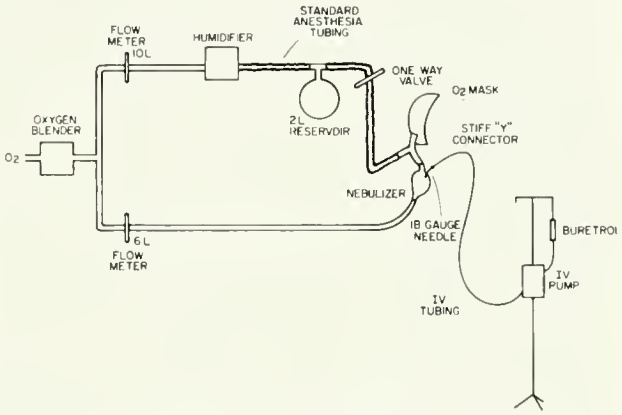


Fig. 4. Apparatus used to administer continuous nebulization therapy. (Reprinted, with permission, from Reference 30.)

Stable Severe COPD

Harrison and Pierce[31] obtained cumulative dose-response curves using salbutamol delivered by MDI (maximum dose 800 μg) or nebulizer (maximum dose 10 mg) in 10 chronic bronchitic and 10 asthmatic patients with severe airflow obstruction. The MDI and nebulizer yielded comparable results for each category of patients with an efficiency ratio of 12.5 to 1 (Fig. 5). However, the dose-response curves were flatter in the bronchitic than in the asthmatic patients, consistent with less-reversible disease in the former population. In stable bronchitic patients, a near-maximal response was achieved with conventional doses of albuterol (200 μg via MDI or 2.5 mg via nebulizer), suggesting that higher maintenance doses may not offer any advantages in the treatment of stable COPD.

Mestitz et al[15] treated 10 clinically stable, moderate-to-severe COPD patients with doses of terbutaline (determined by cumulative dose-response curves) that were higher than those conventionally used (1.25 mg via MDI or 2.5 mg via wet nebulizer). The higher maintenance doses produced modest improvement in lung function and in exercise tolerance (without adverse side effects) compared to standard maintenance aerosol therapy,

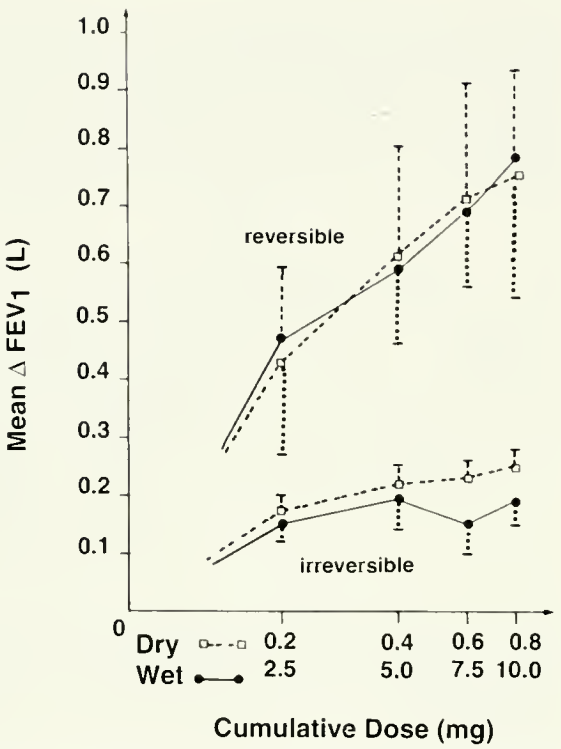


Fig. 5. Cumulative log dose-FEV_1 response relationships [mean (SEM)] for wet (nebulizer) and dry (MDI) albuterol aerosol in patients with reversible airflow obstruction (asthma) and irreversible airflow obstruction (COPD). (Reprinted, with permission, from Reference 31.)

irrespective of the method of aerosol delivery (MDI or nebulizer).

Jenkins et al[32] observed that approximately one half of the 19 patients with severe stable COPD (mean FEV_1 0.55 L) in whom they performed cumulative dose-response curves with albuterol required higher-than-conventional doses (ie, 400-600 μg) to achieve maximal bronchodilation. They recommended the dosing strategy outlined in Table 3 to determine the optimal dose of albuterol for maintenance aerosol therapy in stable COPD. Higher-than-conventional maintenance doses were generally well tolerated and led to improvement in respiratory symptoms and in activity level. No significant differences were noted in response to the two different modes of delivering albuterol aerosol (MDI vs nebulizer). Because of the comparable efficacy of the MDI and wet nebulizer in the management of severe COPD with inhaled beta-adrenergic agonists, the MDI is the preferred mode of aerosol treatment because of its lower cost and greater convenience.

Table 3. Dosing Strategy for Albuterol Aerosol Treatment of Stable COPD[32]

1. Administer albuterol MDI 2 puffs (180 μg) or 2.5 mg/4 mL via power nebulizer.
2. Measure PEFR, FEV_1, VC, and HR 15 and 30 min later and then every 10 min until no further increase in FEV_1 VC, or PEFR.
3. Repeat albuterol MDI 2 puffs or 2.5 mg/mL via nebulizer.
4. Repeat measurements as in Step 2.
5. Repeat process until further drug doses produce no further increase in PEFR, FEV_1, or VC.
6. Administer QID the dose of albuterol producing greatest bronchodilation in any given patient.
7. Assess daily peak flow, symptoms, and extra bronchodilator use.

Dose Requirements for Anticholinergic Bronchodilators

A full discussion of the role of anticholinergic bronchodilator therapy in acute and chronic asthma and COPD is beyond the scope of this paper. The reader is referred elsewhere for a general review of this topic.[33] I will briefly consider the question of how to determine the optimal dose for an anticholinergic bronchodilator.

Only one anticholinergic compound, ipratropium bromide (a polar, water-soluble quaternary derivative of atropine), is approved by the FDA for use as a bronchodilator, specifically in the treatment of COPD. Ipratropium bromide has advantages over atropine sulfate (a fat-soluble, tertiary ammonium compound) mainly because, unlike atropine sulfate, it is poorly absorbed from the respiratory and gastrointestinal tracts and does not cross the blood-brain barrier.[33] Consequently, ipratropium bromide is virtually devoid of the well-known systemic cholinergic side effects of atropine sulfate, such as visual blurring and aggravation of bladder-outlet obstruction. Because ipratropium is

currently available in the U.S. only in the form of an MDI, atropine sulfate solution is used when anticholinergic bronchodilator therapy in the form of a wet aerosol is desired, despite the lack of FDA approval for this use of atropine. The solution form of ipratropium bromide for nebulization therapy is available abroad, but has yet to be approved in the U.S.

Dose-response studies[34] using incremental doses of atropine-sulfate solution (0.005 to 0.1 mg/kg) in children with stable asthma have revealed a plateau maximum after a dose of 0.05 mg/kg; the peak effect occurred 1 hour after inhalation, and the duration of action was as long as 5 hours. Because maximally effective doses of atropine sulfate are likely to be associated with clinically important side effects, smaller doses (0.025 mg/kg, or 1-2 mg in adults) are generally employed. Dose-response curves for nebulized ipratropium bromide in patients with acute asthma have shown 500 μg to be the smallest dose yielding a maximal bronchodilator response,[35] indicating that this compound is more potent than atropine. Cumulative doses of ipratropium by MDI administered to stable patients with either asthma or chronic bronchitis produced a response plateau after 4 inhalations (80 μg) in the asthmatics but after only 2 inhalations (40 μg) in the bronchitics.[36] Because ipratropium is associated with very few side effects, even when administered in considerably larger doses than recommended by the manufacturer (40 μg), a trial of higher-than-recommended doses may be worthwhile under certain circumstances, such as in COPD that is poorly responsive to conventional doses. A common finding of many investigators is that ipratropium is generally less effective than beta-adrenergic agonists for the treatment asthma but more effective than beta-adrenergic agonists for the treatment of COPD.[33]

The administration of ipratropium by MDI or atropine (in solution form) by nebulizer, in combination with inhaled beta-adrenergic agonists, for the treatment of severe acute asthma has been evaluated by several investigators. Most authors[35,37-39] report an additive bronchodilator effect when ipratropium (0.5-1 mg) is combined with large doses of a beta-adrenergic-agonist solution aerosol (albuterol 5-10 mg or fenoterol 1-1.25 mg). The effect of the beta-adrenergic agonist appears to be enhanced when ipratropium is administered 60-120 minutes prior to the beta-adrenergic agonist.[35,38,39] This may be due to a preferential bronchodilator action of the anticholinergic on the large central airways where cholinergic receptors are located in greatest density, thus facilitating delivery of the subsequently administered beta-adrenergic agonist to peripheral sites in the lower respiratory tract where adrenergic influences predominate.[40] In contrast, one group[41] failed to observe that anticholinergics provided any significant added benefit when inhaled beta-adrenergic agonists had already been used in very high, frequent doses for the treatment of acute severe asthma. Other investigators[42] have observed that ipratropium, while not increasing the overall maximal bronchodilator response to a large dose of nebulized albuterol, may prolong the duration of the response.

Available data are conflicting as to whether inhaled beta-adrenergic agonists and ipratropium administered in conventional doses produce additive bronchodilation in stable COPD. However, it is clear that in patients with COPD these two agents, when administered in maximal doses, produce equivalent bronchodilation individually and do not produce greater bronchodilation in combination.[43]

Effective Dosing for Delivery of Bronchodilator Aerosols to Mechanically Ventilated Patients

Delivery of aerosols from both solution nebulizers and MDIs to intubated, mechanically ventilated patients is far less efficient than delivery to spontaneously breathing patients.[44-47] Studies suggest that only 1.2-2.9% of the medication from a jet nebulizer reaches the lungs of the mechanically ventilated patient.[44,46,47] In one of these studies,[47] a higher mean percentage of a given dose (5.65%) was delivered to the lower respiratory tract of intubated, ventilated patients by MDI with holding chamber. However, even this dose is approximately half that delivered by a correctly used MDI to the lungs of spontaneously breathing patients. Possible reasons for the reduced efficiency of aerosol delivery to mechanically ventilated patients include (1) excessive impaction of the aerosolized particles in the curved ETT due

to the turbulent high-flow conditions of mechanical ventilation, (2) growth of hygroscopic particles in the humid ventilator circuit, (3) adsorption of drug to ventilator tubing, and (4) reduced inspiratory hold times leading to loss of aerosol during exhalation.[45,47] Results of a recent bench study[45] suggest that the delivery efficiency of an MDI through an ETT can be improved by using a larger tube size and by activating the MDI into a flowing stream of gas after initiation of inspiration. Recent evidence[48] suggests that the delivery efficiency of an MDI is also influenced by the type of adapter used for delivering the aerosol from the MDI canister into the ETT or ventilator circuit.

It is clear that additional work is needed to determine the optimal method for delivering bronchodilator aerosols to ventilated patients. However, the available data suggest that, in the setting of mechanical ventilation, MDIs are probably more efficient than solution nebulizers but, at best, only about 50% as efficient as MDIs used in spontaneously ventilating patients. Therefore, the dose of a bronchodilator delivered by MDI to an intubated patient should be at least double that used for treatment of the non-intubated patient. However, even doubling the dose may not suffice because patients mechanically ventilated for treatment of severe airflow obstruction are likely to be more refractory to bronchodilator therapy. This may account, at least in part, for the failure of some investigators[45,47] to observe physiologic evidence of bronchodilator effectiveness in mechanically ventilated patients receiving aerosol therapy.

Summary

Optimally effective dosing with aerosolized bronchodilators depends on the potency of the bronchodilator agent, the method of aerosol delivery (which, in turn, determines the dose delivered to the lung), and the response characteristics of the patient. Therefore, optimal doses may differ from those recommended by manufacturers, and will vary between and within delivery devices (depending on the method of use) and between and within patients (depending on disease type, severity, and stability).

In acute severe asthma, higher and more frequently administered doses of aerosolized beta-adrenergic agonists are usually required than those recommended by the manufacturers. The precise dosing regimen is best determined by individual titration based on frequent clinical assessment, including auscultation and serial measurements of peak expiratory flow. Aerosol therapy with large doses of a beta-adrenergic agonist administered at frequent intervals or continuously, if necessary, is as efficacious as treatment with parenteral beta-adrenergic agonists and has less potential for serious systemic toxicity. Nebulized anticholinergics appear to add to the benefit of beta-adrenergic-agonist aerosol therapy in the treatment of severe acute asthma, particularly when the administration of the anticholinergic bronchodilator precedes that of the beta-adrenergic agonist.

Delivery of aerosols from both solution nebulizers and MDIs to intubated, mechanically ventilated patients is far less efficient than delivery of aerosols to spontaneously breathing patients. This is probably due to excessive losses of the drug in the curved endotracheal tube and ventilator circuit. Although further work is needed to determine the optimal method for delivering aerosolized bronchodilators to ventilated patients, preliminary data suggest that MDIs are more efficient than solution nebulizers but only about 50% as efficient as MDIs in non-intubated patients. In the treatment of the intubated patient with obstructive pulmonary disease, aerosolized bronchodilators should be given in larger than conventional doses because of the relative inefficiency of available delivery devices for this purpose and because the mechanically ventilated patient is often relatively refractory to bronchodilator therapy.

REFERENCES

1. Brittain RT, Dean CM, Jack D. Sympathomimetic bronchodilator drugs. Pharmacol Ther B 1976;2(3):423-462.
2. Tashkin DP. Measurement and significance of the bronchodilator response. In: Jenne JW, Murphy S, eds. Drug therapy for asthma, research and clinical practice. New York: Marcel Dekker, 1987:535-613.
3. James AL, Paré PD, Hogg JC. The mechanisms of airway narrowing in asthma. Am Rev Respir Dis 1989;139:242-246.

4. Orehek J, Nicoli MM, Delpierre S, Beaupre A. Influence of the previous deep inspiration on the spirometric measurement of provoked bronchoconstriction in asthma. Am Rev Respir Dis 1981;123:269-272.
5. Bouhuys A, van de Woestijne KP. Mechanical consequences of airway smooth muscle relaxation. J Appl Physiol 1971;30:670-676.
6. Woolcock AJ, Read J. Lung volumes in exacerbations of asthma. Am J Med 1966;41:259-273.
7. Jenne JW, Tashkin DP. Bronchodilators as a bronchial challenge: a critical assessment. In: Spector SL, ed. Provocative challenge procedures: bronchial, oral, nasal and exercise, Vol II. Boca Raton FL: CRC Press, 1983:19-73.
8. Ahrens RC, Harris JB, Milavetz G, Annis L, Ries R. Use of bronchial provocation with histamine to compare the pharmacodynamics of inhaled albuterol and metaproterenol in patients with asthma. J Allergy Clin Immunol 1987;79:876-882.
9. Torphy TJ, Rinard GA, Rietow MG, Mayer SE. Functional antagonism in canine tracheal smooth muscle: inhibition by methacholine of the mechanical and biochemical responses to isoproterenol. J Pharmacol Exper Ther 1983;227:694-699.
10. Torphy TJ. Differential relaxant effects of isoproterenol on methacholine-versus-leukotriene D4-induced contraction in the guinea-pig trachea. Eur J Pharmacol 1984;102:549-553.
11. Speizer FE, Doll R, Heaf P, Strang LB. Investigation into use of drugs preceding death from asthma. Br Med J 1968;1:339-343.
12. Anonymous. Fatal asthma (editorial). Lancet 1979;2:337-338.
13. Nelson HS, Spector SL, Whitsett TL, George RB, Dwek JH. The bronchodilator response to inhalation of increasing doses of aerosolized albuterol. J Allergy Clin Immunol 1983;72:371-375.
14. Lewis RA. Inhalation drugs in asthma management: state of the art, factors affecting delivery, and clinical response to inhaled drugs. NER Allergy Proc 1984;5(1):23-33.
15. Mestitz H, Copland JM, McDonald CF. Comparison of outpatient nebulized vs metered dose inhaler terbutaline in chronic airflow obstruction. Chest 1989;96:1237-1240.
16. Prior JG, Nowell RV, Cochrane GM. High-dose inhaled terbutaline in the management of chronic severe asthma: comparison of wet nebulisation and tube-spacer delivery. Thorax 1982;37:300-303.
17. Sears MR, Taylor DR, Print CG, Lake DC, Li Q, Flannery EM, et al. Regular inhaled beta agonist treatment in bronchial asthma. Lancet 1990;336:1391-1396.
18. Kraan J, Koëter GH, Mark TW, Sluiter HJ, de Vries K. Changes in bronchial hyperreactivity induced by 4 weeks of treatment with antiasthmatic drugs in patients with allergic asthma: a comparison between budesonide and terbutaline. J Allergy Clin Immunol 1985;76:628-636.
19. Benton G, Thomas RC, Nickerson BG, McQuitty JC, Okikawa J. Experience with a metered-dose inhaler with a spacer in the pediatric emergency department. AJDC 1989;143:678-681.
20. Kelly HW, McWilliams BC, Katz R, Murphy S. Safety of frequent high-dose nebulized terbutaline in children with acute severe asthma. Ann Allergy 1990;64(Feb,Part II):229-233.
21. Robertson CF, Smith F, Beck R, Levison H. Responses to frequent low doses of nebulized salbutamol in acute asthma. J Pediatr 1985;106:672-674.
22. Wood DW, Downs JJ, Scheinkopf H, Lecks HI. Intravenous isoproterenol in the management of respiratory failure in childhood status asthmaticus. J Allergy Clin Immunol 1972;50:75-81.
23. Cotton EK, Parry W. Treatment of status asthmaticus and respiratory failure. Pediatr Clin North Am 1975;22:163-171.
24. Kurland G, Williams J, Lewiston NJ. Fatal myocardial toxicity during continuous infusion intravenous isoproterenol therapy of asthma. J Allergy Clin Immunol 1979;63:407-411.
25. Matson JR, Loughlin GM, Strunk RC. Myocardial ischemia complicating the use of isoproterenol in asthmatic children. J Pediatr 1978;92:776-778.
26. Maguire JF, Geha RS, Umetsu DT. Myocardial specific creatine phosphokinase isoenzyme elevation associated with intravenous isoproterenol therapy of childhood asthma (abstract). J Allergy Clin Immunol 1986;77(1, Part 2):A109.
27. Lawford P, Jones BJM, Milledge JS. Comparison of intravenous and nebulised salbutamol in initial treatment of severe asthma. Br Med J 1978;1:84.
28. Van Renterghem D, Lamont H, Elinck W, Pauwels R, Van Der Straeten M. Intravenous versus nebulized terbutaline in patients with acute severe asthma: a double-blind randomized study. Ann Allergy 1987;59:313-316.
29. Thiringer G, Svedmyr N. Comparison of infused and inhaled terbutaline in patients with asthma. Scand J Respir Dis 1976;57:17-24.
30. Moler FW, Hurwitz ME, Custer JR. Improvement in clinical asthma score and P_{aCO_2} in children with severe asthma treated with continuously nebulized terbutaline. J Allergy Clin Immunol 1988;81:1101-1109.
31. Harrison BA, Pierce RJ. Comparison of wet and dry aerosol salbutamol. Aust NZ J Med 1983;13:29-33.
32. Jenkins SC, Heaton RW, Fulton TJ, Moxham J. Comparison of domiciliary nebulized salbutamol and salbutamol from a metered-dose inhaler in stable chronic airflow limitation. Chest 1987;91:804-807.
33. Gross NJ. Ipratropium bromide. N Engl J Med 1988;319:486-494.
34. Cavanaugh MJ, Cooper DM. Inhaled atropine sulfate: dose response characteristics. Am Rev Respir Dis 1976;114:517-524.

35. Marlin GE, Bush DE, Berend N. Comparison of ipratropium bromide and fenoterol in asthma and chronic bronchitis. Br J Clin Pharmacol 1978;6:547-549.
36. Rebuck AS, Chapman KR, Abboud R, Paré PD, Kreisman H, Walkone N, et al. Nebulized anticholinergic and sympathomimetic treatment of asthma and chronic obstructive airways disease in the emergency room. Am J Med 1987;82:59-64.
37. Ward MJ, Fentem PH, Roderick Smith WH, Davies D. Ipratropium bromide in acute asthma. Br Med J 1981;282:598-600.
38. Bryant DH. Nebulized ipratropium bromide in the treatment of acute asthma. Chest 1985;88:24-29.
39. Leahy RC, Gomm SA, Allen SC. Comparison of nebulized salbutamol with nebulized ipratropium bromide in acute asthma. Br J Dis Chest 1983;77:159-163.
40. Ingram RH Jr, Wellman JJ, McFadden ER Jr, Mead J. Relative contributions of large and small airways to flow limitation in normal subjects before and after atropine and isoproterenol. J Clin Invest 1977;59:696-703.
41. Karpel JP, Appel D, Breidbart D, Fusco MJ. A comparison of atropine sulfate and metaproterenol sulfate in the emergency treatment of asthma. Am Rev Respir Dis 1986;133:727-729.
42. Higgins RM, Stradling JR, Lane DJ. Should ipratropium bromide be added to beta-agonists in treatment of acute severe asthma? Chest 1988;94:718-722.
43. Easton PA, Jadue C, Dhingra S, Anthonisen NR. A comparison of the bronchodilating effects of a beta-$_2$ adrenergic agent (albuterol) and an anticholinergic agent (ipratropium bromide) given by aerosol alone or in sequence. N Engl J Med 1986;315:735-739.
44. Fraser I, DuVall A, Dolovich M, Newhouse MT. Therapeutic aerosol delivery in ventilator systems (abstract). Am Rev Respir Dis 1981;123(4, Part 2):107.
45. MacIntyre NR, Silver RM, Miller CW, Schuler F, Coleman RE. Aerosolized delivery in intubated, mechanically ventilated patients. Crit Care Med 1985;13:81-84.
46. Crogan SJ, Bishop MJ. Delivery efficiency of metered dose aerosols given via endotracheal tube. Anesthesiology 1989;70:1008-1010.
47. Fuller HD, Dolovich MB, Posmituck G, Wong Pack W, Newhouse MT. Pressurized aerosol versus jet aerosol delivery to mechanically ventilated patients. Am Rev Respir Dis 1990;141:440-444.
48. Larson RP, Bishop MJ, Buschman DL. Metered dose inhaler actuator adapters: a comparison of particle size and drug delivery through an endotracheal tube (abstract). Respir Care 1989;34:1029.

Dosing Strategies for Aerosol Delivery to the Lung Parenchyma, with Specific Recommendations for Pentamidine

Heinrich Matthys MD and Rosa Herceg MD

Factors Affecting Delivery and Deposition

Particles with a mass median aerodynamic diameter (MMAD) of 1-3 μm are optimal for drug deposition in the peripheral airways and the alveolar space. Because of the relationship between radius and volume ($V \approx r^3$) larger particles contribute more to the mass of an aerosol and hence to therapy than do smaller droplets. The efficiency of aerosol therapy depends on

- physiocochemical properties of the solution,
- aerosol generator and propellant,
- application and connection system,
- breathing pattern and airway geometry,
- regional distribution of deposition,
- local drug clearance and elimination, and
- biologic properties and drug side effects.

Physicochemical Properties of the Aerosol Solution

For solutions with the physicochemical properties of water, it is easy to measure MMAD for most nebulizers. However, with pentamidine solutions, the physical properties change according to the concentration (viscosity of 300-mg solution = 1.19, and the 600-mg solution = 1.37, in relation to water). Therefore we obtain different particle spectra for different amounts of pentamidine dissolved in the same amount of water. With increasing nebulization periods (thus, increased inhalation time) the pentamidine solution generally becomes more viscous, which leads to a decrease in pulmonary deposition fraction. This is especially true for ultrasonic nebulizers, which are more affected by the viscosity of the solution than are jet nebulizers.

Table 1 shows the percent change in lung deposition due to the higher viscoelastic properties of solutions of 600 mg compared to 300 mg of pentamidine in 6 mL water aerosolized with an ultrasonic nebulizer (Portasonic, DeVilbiss Health Care Inc) and two jet nebulizers Pari IS 2 and Respirgard II (Marquest Medical Products Inc). With the Portasonic, after 20 minutes of inhalation of the 300-mg pentamidine solution, a pulmonary deposition of 46.9 mg was observed, which decreased to 16.9 mg with the 600-mg solution. On the other hand, with the mechanical nebulizer Pari IS 2 we observed an increase in pulmonary deposition from 10 to 43.7 mg and with the Respirgard II from 13.3 to 25.3 mg with increasing pentamidine concentrations.[1] Table 2 shows different amounts of pulmonary deposition with different nebulizers, operating characteristics, and breathing patterns.[1-3] From this data it appears clear that when drugs in solution change the physicochemical properties of the solution relative to water, the change can lead to completely different particle spectra and hence different deposition patterns as a function of the viscoelastic properties of the solution. The phy-

Dr Matthys is the Medical Director of the Division of Pneumonology, Department of Internal Medicine, University Hospital, Freiburg, Germany. Dr Herceg (from the Semmelweiss University in Budapest, Hungary) was a research fellow working with Dr Matthys when this paper was written.

A version of this paper was presented by Dr Matthys during the Consensus Conference on Aerosol Delivery, sponsored by the American Association for Respiratory Care, the American Respiratory Care Foundation, and the journal RESPIRATORY CARE, January 10-12, 1991, in Cancun, Mexico.

Reprints: Henrich Matthys MD, Artzlichter Direktor, Abteilung Pneumonologie, Robert-Koch Klinik, Universistat D7800, Freiburg, Germany.

Table 1. Distribution of Inhaled Aerosolized Pentamidine within the Lung, Detected by Radioactive Tracer in 6 Subjects*

	300-mg Pentamidine Isethionate in 6 mL H_2O % (SD)		
Nebulizer	Respirgard II	Pari IS 2	Portasonic
Lung deposition	13.32 mg = 100%	10.02 mg = 100%	46.92 mg = 100%
Tracheal	2.16 (0.41)	3.40 (0.89)	3.47 (2.74)
Central	50.67 (3.62)	49.60 (3.44)	51.00 (4.47)
Peripheral	47.33 (3.72)	47.60 (2.70)	46.45 (4.29)
Upper fields	44.17 (4.36)	46.20 (3.03)	46.67 (3.39)
Lower fields	55.83 (4.36)	53.80 (3.03)	53.33 (3.89)
	600-mg Pentamidine Isethionate in 6 mL H_2O % (SD)		
Nebulizer	Respirgard II	Pari IS 2	Portasonic
Lung deposition	25.28 mg = 100%	43.68 mg = 100%	16.92 mg = 100%
Tracheal	2.21 (0.38)	4.08 (0.62)	5.16 (0.18)
Central	53.26 (4.62)	49.60 (3.44)	51.00 (4.47)
Peripheral	47.33 (3.02)	54.35 (4.48)	60.41 (5.52)
Upper fields	46.17 (5.16)	46.67 (1.53)	54.06 (3.16)
Lower Fields	53.55 (3.66)	53.33 (1.53)	46.19 (1.42)

*Adapted, with permission, from Reference 1.

sicochemical properties (pH and osmolarity) also determine the number and intensity of side effects. For example, large particles deposited in the laryngotracheal region trigger the cough reflex. Distilled water leads to bronchial constriction, especially in asthmatic patients. This is the reason why bronchodilator inhalation prior to small-droplet aerosol therapy reduces cough and bronchoconstriction resulting from the inhalation of aerosols of different medicaments.[3]

Aerosol Generators and Propellants

Most aerosol generators are either of mechanical (jet) or ultrasonic design. The mist density of ultrasonic nebulizers is generally greater than that of the jet nebulizers. As nebulization (and thus inhalation) time increases, the problems associated with aerosolization of highly viscous drug solutions increase. We have observed that the performance of both mechanical (jet) and ultrasonic nebulizers are affected, particularly when they are used repeatedly without adequate service. The particle spectra can also be changed by the presence of spacers and baffles used to facilitate inhalation and to avoid dispersal of bigger particles generally deposited in the outlet tubings and upper airways of the patient (Table 2).[1-3]

Application and Connection Systems

Aerosols for lung deposition should always be administered through a mouthpiece because the nose is an excellent aerosol filter. When a face mask is used, breathing through the nose should be avoided by applying a nose clip. Longer mouthpieces increase comfort and dead space and decrease the delivery of bigger particles with their related side effects. Some nebulizers deposit a great deal of medication in the connection system, especially when aerosolization is continuous rather than being triggered by the inhalation maneuver. Such triggers exist for the FISONeb and Pari IS 2, for example, but not for the Respirgard II and Portasonic. The extracorporeal deposition in the tubing, nebulizer system, storage bag, expiratory filters, and valves is generally greater than the total corporeal deposition (Table 3).

Table 3. Corporeal and Extracorporeal Distribution of Inhaled Pentamidine Detected by Radioactive Tracer*

	300-mg Pentamidine Isethionate in 6 mL H_2O		
Nebulizer	Respirgard II	Pari IS 2	Portasonic
Lung deposition %	4.44 (1.89)	3.03 (1.36)	15.64 (5.73)†
Oropharynx %	0.18 (0.9)	0.82 (0.92)	0.56 (0.31)
Stomach %	0.15 (0.09)	1.70 (3.03)	2.14 (1.01)
Extracorporeal %‡	95.30 (5.61)	94.50 (5.16)	81.80 (4.92)
	600-mg Pentamidine Isethionate in 6 mL H_2O		
Nebulizer	Respirgard II	Pari IS 2	Portasonic
Lung deposition %	4.38 (1.78)	7.27 (9.14)	2.82 (1.04)
Oropharynx %	0.20 (0.07)	0.38 (0.20)	0.42 (0.13)
Stomach %	0.18 (0.09)	0.82 (1.12)	1.70 (0.90)
Extracorporeal %	95.20 (5.61)	91.50 (7.67)	95.10 (7.19)

*Adapted, with permission, from Reference 1. Values are mean (SD).
† $p < 0.05$.
‡ Extracorporeal = remaining percentage deposited in aerosol generator, tubes, and filters.

Regional Aerosol Deposition

In normal subjects, the total corporeal deposition is known to vary even with the same nebulizer.[4] Stomach deposition increases with airway resistance and aerophagia due to dyspnoea. The amount of oropharyngeal deposition reflects mainly the particle size and high inspiratory flowrates. Central bronchial deposition increases with increasing particle size (5-10 μm) and airway obstruction. Upper- and lower-lung-field deposition is equal if the aerosol is inhaled during slow-vital-capacity breathing. Normal tidal breathing at functional residual capacity increases lower-lung-field deposition. This may be the reason that *Pneumocystis carinii* pneumonia (PCP) has been observed in the upper lung fields despite pentamidine prophylaxis.[5]

Local Drug Clearance

Pulmonary drug clearance depends on the deposition site of the aerosol in the respiratory tract, the physiologic properties of the drug, and the local disease state. Active transport, passive diffusion, phagocytosis, storage of the drug in cells (macrophages), and regional (lymphatic, arterial, and venous) tissue perfusion determine recycling and local action of the drug (Fig. 1). Bronchial deposition with local absorption in the central airways leads to recirculation through the right heart or directly into the alveolar capillaries, a mechanism that seems to be important for bronchodilator therapy with $beta_2$ agonists. Alveolar deposition and diffusion into the pulmonary circulation (vasa publica) lead to dilution of the substance in the

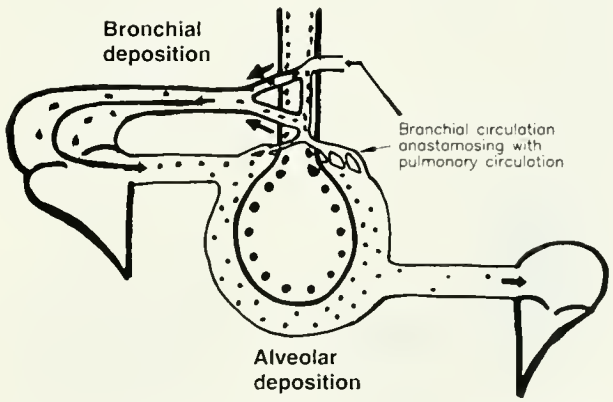


Fig. 1. Recycling possibilities in the blood of deposited particles in the bronchial tree and the alveolar space. Bronchial deposition leads mainly to absorption and dilution of the particles into the pulmonary circulation; alveolar deposition leads to absorption and dilution into the systemic circulation.

systemic circulation before recycling of the drug into the pulmonary artery is observed. This recirculation generally has no additional effect and seems to be unimportant for aerosolized drug delivery to the lung parenchyma. Pentamidine has a half life of about 1 month in the lung. The mechanism of its extraordinary selectivity for the lung by aerosol routes is unknown.

Biologic Properties and Drug Side Effects

Pentamidine shows a high preference for the lung parenchyma when applied by aerosol in contrast to intravenous or oral administration. Thus, after aerosol application, the pentamidine concentration in the lung has been found to be 10-100 times higher than after intravenous administration. Bronchoalveolar lavage (BAL) measurements showed concentrations of about 700 ng/mL.[6,7] This special affinity of pentamidine leads to therapeutic concentrations over weeks and to an accumulation of the drug in the lung when given at weekly or monthly intervals (Fig. 2[8]). Despite the often inefficient application of pentamidine by different nebulizers and poor patient compliance, this selective accumulation in the lung makes the drug ideal for aerosol therapy. It probably also explains the high protective effect of inhaled pentamidine against *Pneumocystis carinii* infection and the low therapeutic effect against *P carinii* pneumonia. Aerosolized pentamidine produces few side effects,

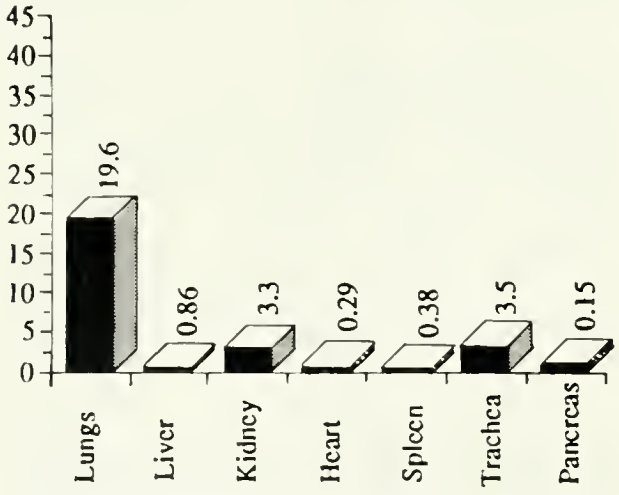


Fig. 2. Mean concentrations of pentamidine (μg/g) in various organs of the rat at Day 1 after administration of a single dose by aerosol. (Reprinted, with permission, from Reference 8.)

and has almost no apparent effect on other organs (Table 4[2]). The possible mechanisms of the selective pentamidine accumulation in th lung deserve investigation to develop more drugs for selective aerosol therapy of the lung.

Therapeutic Relapses

Noncompliant patients are most frequently drug abusers. Noncompliance was the main cause of therapeutic relapses in a controlled study with 29 patients on primary and 16 on secondary prophylactic pentamidine treatment. All had CD-4 lymphocyte counts below 200/μL. *Pneumocystis carinii* pneumonia was observed only in the patients who did not show up regularly for the treatment sessions.

We have observed that inadequate aerosol application often occurs with inexperienced and uninstructed patients on home treatment on a "do-it-yourself" basis.

A complete breakdown of the immune system and recurrent PCP increase the risk of relapses (Table 5[9]). PCP was for a long time the most common cause of death and pneumonia in immunocompromised patients. Pentamidine aerosol prophylaxis has lead to a PCP reduction to the extent that today cytomegalovirus, mycobacterioses, and fungal infections including toxoplasmosis may have become the more frequent complications in AIDS patients and other immunocompromised subjects.

P carinii resistance to pentamidine has not been described, and it is not known whether such resistance is developing. Aerosol therapy for manifest PCP is obviously less effective than for prophylaxis, and PCP requires additional treatment with oral or intravenous cotrimoxazole or pentamidine. A loading dose of weekly aerosolized pentamidine (300 mg) in the first month is recommended.

In Conclusion

The pentamidine concentration of choice for PCP prophylaxis in patients with a helper-lymphocyte CD-4 count below 200/μL is 300 mg in 6 mL of distilled water. In our experience, the inhalation time of 20 minutes can be reduced to 5-10 min without a loss of security if vital capacity breathing (rather than normal tidal breathing) is

Table 4. Side Effects Associated with Aerosolised Pentamidine Inhalation Assessed Using Visual Analogue Scales*

Side Effect	Respirgard II	Centimist	System 22 Mizer	Mizer-Separator	Mizer-Optimist 2	FISONeb	Portasonic	Samsonic
Breathlessness	9 (5)†	11 (4)	35 (8)‡	5 (2)	6 (1)	11 (3)	30 (8)	19 (7)
Nausea	8 (5)	9 (2)	32 (8)	4 (1)	10 (6)	22 (10)	40 (10)‡	11 (5)
Burning	8 (2)	21 (7)	62 (5)‡	10 (6)	16 (10)	45 (10)	63 (8)	17 (9)
Taste	34 (5)	52 (5)	70 (18)‡	15 (4)	19 (7)	61 (8)‡	73 (7)	30 (8)
Overall impression	31 (5)	39 (7)	71 (5)‡	11 (3)	29 (9)	47 (7)	70 (6)‡	30 (7)

*Adapted, with permission, from Reference 2.
† Analogue scale values range from 0 and 100, with higher numbers indicating more marked side effects. Values are mean (SD).
‡ $p < 0.05$ vs Respirgard II by Wilcoxon rank sum test.

performed with an inspiratory aerosol demand system. Such a nebulizer system with a storage bag of about 5-10 L reduces (1) the amount of drug needed, (2) costs, and (3) side effects. The vital capacity breathing pattern appears also to reduce the incidence of PCP upper-lobe involvement in patients receiving prophylaxis with aerosolized pentamidine.

Ultrasonic and jet nebulizers that allow lung deposition of at least 5-mg pentamidine per session every month are sufficient for PCP prophylaxis. Pulmonary deposition is best assessed with radioactive tracers added to the nebulizer solution. Direct measurements on patients give better clinical information than in-vitro studies on lung models. The nebulizer characteristics are less important than regular and well-guided aerosol application because aerosolized pentamidine accumulates in the lung selectively to levels 10-100 times higher than those attained by intravenous administration. It is not likely that other drugs like ribavirin, alpha$_1$-antitrypsin, and especially conventional antibiotic aerosols will be as easy to handle as are pentamidine aerosols.

Table 5. Number and Percent of *Pneumocystis carinii* Pneumonia (PCP) Relapses as a Function of Previous PCP Episodes*

	Number (%) of Previous PCP Episodes		
	0	1	2
Patients under pentamidine prophylaxis	241	70	19
Number of relapses (%)	8(3)	5(7)	4(21)

*Adapted, with permission, from Reference 9.

REFERENCES

1. Matthys H, Herceg R. Lung deposition of 300 and 600 mg pentamidine, inhaled with 3 different inhalers. Med Klin 1990;85(2 Suppl):251-254.
2. O'Doherty M, Thomas S, Page C, Nunan T, Bateman N. Pulmonary deposition of aerosolized pentamidine (AP): comparison of 7 nebulizers. Eur Respir J 1990;3(10, Suppl):120S.
3. Simonds AK, Newman SP, Johnson MA, Talaee N, Lee CA, Clarke SW. Alveolar targeting of aerosol pentamidine. Am Rev Respir Dis 1990;141:827-829.
4. Matthys H, Köhler D. Pulmonary deposition of aerosols by different mechanical devices. Respiration 1985;48: 269-276.
5. Scannell KA. Atypical presentation of *Pneumocystis carinii* pneumonia in a patient receiving inhalational pentamidine. Am J Med 1988;85:881-884.
6. Montgomery AB, Debs RJ, Luce JM, Corkery KJ, Turner J, Brunette EN, et al. Selective delivery of pentamidine to the lung by aerosol. Am Rev Respir Dis 1988;137:477-478.
7. Montgomery AB, Luce JM, Turner J, Lin ET, Debs RJ, Corkery KJ, et al. Aerosolized pentamidine as sole therapy for *Pneumocystis carinii* pneumonia in patients wit acquired immunodeficiency syndrome. Lancet 1987;2: 480-483.
8. Farinotti R, Certain A, Gerard PM, Bidault R, Claire B, Dautzenberg B. Pharmacokinetics of pentamidine following aerosolization. JAMA 1990; Supp 2:39-43.
9. Staszewski S. Prophylaxe der PCP mit Pentamidin Aerosol. PCP Abstracts, 3. Deutscher Aids-Kongress Hamburg, Nov 1990.

Aerosol Therapy in Children

R Michael Sly MD

Introduction

Therapeutic aerosols prescribed for children comprise beta-adrenergic agonists, antimuscarinics, cromolyn sodium, adrenal corticosteroids, antiviral agents, antibiotics, mucolytics, and pentamidine. Established efficacy and safety vary widely among different compounds.

Published evidence of efficacy and safety recommends use of many of these drugs in children despite lack of labeling as safe and effective in children because insufficient data have been submitted to the United States Food and Drug Administration (FDA).[1] Lack of approval by the FDA should not, however, be misconstrued as disapproval. Clinicians who prescribe for children should avoid the use of drugs contraindicated because research has indicated lack of safety or efficacy in children, but optimal management often requires the use of drugs not labeled for use in children. The dosages of such drugs, and the appropriate precautions, must be determined by published evidence and expert opinion.[1]

Beta-Adrenergic Agonists

There is general agreement that inhaled beta-adrenergic agonists are the treatment of choice for acute asthma in children as well as adults.[2-7] Inhaled beta agonists are at least as effective as epinephrine administered by subcutaneous injection, and inhalation therapy elicits fewer adverse effects.[8-10]

However, there is much less agreement about optimal dosage for children.[5] This uncertainty is due to a dearth of dose-response studies in children and lack of labeling for use in children.

Treatment of acute asthma in children 6-17 years of age with nebulized albuterol, 0.15 mg/kg (maximum 5 mg) followed by 0.05 mg/kg (maximum 1.7 mg), every 20 minutes for 2 hours is safe and effective.[11] The 0.5% albuterol solution was diluted with 2 mL 0.9% saline, and administered through a Hudson Up-Draft II Neb-U-Mist nebulizer with a continuous oxygen flow of 5-6 L/min. Improvement in FEV_1 and in wheezing was significantly better than in children who received 0.15 mg/kg every hour in this parallel study.

Treatment with the larger dose of 0.15 mg/kg (maximum 5 mg) every 20 minutes for 2 hours is even more effective and nearly as safe.[12] Comparison of this regimen with 0.15 mg/kg followed by 0.05 mg/kg every 20 minutes in a randomized, double-blind study of 5- to 17-year-old children disclosed significantly better improvement in FEV_1 with the larger dosage. Albuterol was diluted with 3 mL 0.9% saline and delivered by a WhisperJet nebulizer at a flowrate of 6-7 L/min with a face mask. There was no significant difference in the increase in mean heart rates in the two groups (16% in the high-dose group, 20% in the low-dose group). Serum potassium concentrations decreased a mean of 19-20% in both groups. Eight children in the high-dose group and four in the low-dose group experienced tremor and hyperactivity; three in the high-dose group and one in the low-dose group vomited.

An even larger dose of 0.3 mg/kg (maximum 10 mg) is more effective than 0.15 mg/kg (maximum

Dr Sly is Chairman, Allergy and Immunology, Children's National Medical Center, and Professor of Pediatrics, The George Washington University School of Medicine and Health Sciences, Washington, District of Columbia.

A version of this paper was presented by Dr Sly at the Consensus Conference on Aerosol Delivery, sponsored by the American Association for Respiratory Care, the American Respiratory Care Foundation, and the journal RESPIRATORY CARE, January 10-12, 1991, in Cancun, Mexico.

Reprints: R Michael Sly MD, Children's National Medical Center, 111 Michigan Ave NW, Washington DC 20010-2970.

5 mg) and apparently safe when administered three times at hourly intervals.[13] Albuterol was diluted with 0.9% saline to 3.5-4.5 mL and administered by WhisperJet nebulizer and face mask at an oxygen flowrate of 6-7 L/min. The randomized, double-blind study of 5- to 17-year-old children with acute asthma and initial FEV_1 less than 60% predicted normal disclosed significantly better improvement in FEV_1 at the higher dosage. Heart rates increased a mean of 34% in the high-dose group and 25% in the lower-dose group. Serum potassium concentration decreased a mean of 25% in the high-dose group and 22% at the lower dosage. There were no cardiac arrhythmias.

Administration of inhalation therapy at intervals of 20 minutes approaches continuous nebulization, but there have been no controlled studies of continuous nebulization treatment in children. Uncontrolled studies of continuous nebulization of terbutaline in children have indicated safety and effectiveness.[14,15] A retrospective study of responses of 12 children with severe asthma (progressive despite treatment with subcutaneous injections of epinephrine, intermittent inhalation of beta agonists, and intravenous theophylline and adrenal corticosteroids) disclosed improvement in blood gases and respiratory rates with decreases in pulse rates when the children were treated with continuous nebulization of terbutaline.[14] The children, 2-13 years of age, received doses of 1-12 mg terbutaline per hour by face mask and Intec nebulizer with oxygen flowrates of 5-10 L/min adjusted so that nebulization of 1/4 of each hourly dose lasted 15 minutes. Continuous nebulization was administered for 1- 24 hours. There were no adverse effects.

Analysis of the results of treatment of acute asthma with impending respiratory failure in 19 children, 1-14 years of age, during 27 admissions to the hospital, also confirmed the safety and efficacy of continuous nebulization of terbutaline.[15] Treatment had included intravenously administered methylprednisolone and theophylline and nebulized terbutaline, 2 mg, at hourly intervals. Terbutaline was nebulized at a rate of 4 mg/hour with an apparatus that consisted of an intravenous pump that delivered the solution from a burette to a Raindrop nebulizer driven by an oxygen flowrate of 6 L/min. Nebulization continued for 3-37 hours. Mean heart rates, P_{aCO_2}, and clinical asthma scores decreased. There were no adverse effects with the possible exception of transient aberrantly conducted beats in a single patient without any change in heart rate or blood pressure.

Others have described use of a pressure-line adapter to connect a WhisperJet nebulizer to a face mask and delivery of solution from an infusion pump to the elbow of the pressure-line adapter to facilitate administration of continuously nebulized albuterol.[16] No data have been published to verify effectiveness in children of the single system for continuous nebulization available commercially—HEART Large Volume Medication Nebulizer.

There has been only a single dose-response study of nebulized terbutaline in children.[17] The study of 20 children, 8-17 years of age, indicated that doses of 0.2, 0.3, and 0.4 mg/kg (maximum 20 mg) were safe and effective, but single doses of 0.4 mg/kg were repeated only once at 4 hours in 4 children.

Nebulized albuterol is safe and effective for the treatment of asthma, even in most infants as young as 5-24 months of age at a dose of 0.15 mg/kg diluted with 3 mL normal saline (WhisperJet nebulizer, oxygen flowrate 6 L/min).[18]

Much smaller doses of albuterol are effective when delivered by metered dose inhaler (MDI). Doses of 200 μg can elicit bronchodilation for as long as 6 hours without significant adverse effects in children 9-16 years of age.[19]

Protection against induction of bronchoconstriction may have greater relevance to clinical value of a drug than duration of bronchodilation after administration of the beta agonist, which may be due partly to failure of bronchoconstriction to recur after its relief. Periodic challenge with exercise, for example, has indicated that inhaled albuterol (200 μg, MDI) can prevent exercise-induced bronchoconstriction in many asthmatic children for as long as 6 hours after treatment,[20] whereas inhaled metaproterenol (1,300 μg via MDI) does not protect most as long as 2 hours.[20,21]

Use of a spacer tube or chamber can enhance delivery of beta agonists to the lungs in children with poor technique in use of MDIs,[22] although most devices offer no advantage to children with proper

technique.[23] Comparison of responses to slow inhalation of albuterol, 200 μg, from an MDI followed by breath-holding in 20 asthmatic children with inhalation from InspirEase, Aerochamber, and an aerosol bag that consisted of a plastic, 1-quart storage bag with a mouthpiece at one corner within which the MDI was actuated, disclosed similar bronchodilation for all 4 methods of delivery.[22] Use of the chambers elicited significantly better improvement in FEV_1 than the MDI alone in 6 patients with poor coordination of inhalation with actuation of the MDI or shallow inspirations and failure to hold the breath.

Such chambers also permit use of MDIs in children as young as 3 years of age.[24,25] Fitting a chamber with a face mask can permit effective delivery of medication from an MDI to even younger children. Significant improvement in specific conductance followed inhalation of ipratropium bromide from a face mask attached to a Nebuhaler in 7 of 8 wheezing infants, 6-13 months of age.[26]

Use of a 750-mL cone spacer can improve response to inhaled beta agonists in asthmatic children. A randomized, double-blind, crossover study of inhalation of fenoterol, 200 μg, from an MDI with 750-mL cone spacer, and from an air-driven Bennett nebulizer with airflow 6-8 L/min in 10 asthmatic children (7-18 years of age), disclosed significantly better improvement in FEV_1 after inhalation from the spacer than with either of the other methods.[27] There was no significant difference between responses to use of the MDI alone and nebulization of the same dose.

Treatment of acute asthma in children by MDI with the 750-mL Nebuhaler may also be more effective than by nebulization. In a double-blind, crossover study of 21 children (ages 7-14 years) each received terbutaline, 0.1 mg/kg by MDI with a Nebuhaler or by nebulization of terbutaline solution (Pari Inhalier Boy, flow 6 L/min, nebulization synchronized with inhalation).[28] Each crossed over to the other treatment 6 hours later, or sooner if FEV_1 returned to baseline sooner. Improvement in FEV_1 was significantly better after treatment by Nebuhaler and preferred by most children because it took less time.

The high frequency of improper technique in the use of MDIs and concern about potentially adverse effects of chlorofluorocarbon propellants have encouraged development of alternative modes of administration of beta agonists by inhalation. Beta agonists available as dry powders for inhalation have been evaluated in children. A rapid inhalation from either residual volume or functional residual capacity is optimal, unlike optimal inhalation from an MDI, which requires slow inhalation.[29,30] Tilting the head back during inhalation and breath-holding for 10 seconds after inhalation do not improve response to the dry powder.

A randomized, double-blind, crossover study of terbutaline, 500 μg 3 times each day by Turbuhaler and MDI 2 weeks each, in children 6-18 years of age, disclosed no significant differences in symptoms or mean peak expiratory flowrates measured twice daily before and after treatment.[31] Use of the dry powder inhaler was as effective as use of the MDI.

However, evaluation of response to inhalation of salbutamol, 200 μg, by Rotahaler in 15 asthmatic children, 7-14 years of age, indicated significantly less improvement in FEV_1 for inhalation at 30-50 L/min than at 60-120 L/min.[29] Peak inspiratory flowrates during acute airway obstruction were less than 50 L/min in 9 of 13 asthmatic children 6-12 years of age, indicating that they could expect less than optimal response to inhalation of salbutamol by Rotahaler at such critical times.[29] Although the mechanism of reduced responsiveness to salbutamol delivered by Rotahaler at slow flowrates is unknown, this may limit its use in young, asthmatic children.

Furthermore, it may prove difficult for patients who are receiving two different drugs by inhalation to master and to use regularly two entirely different inhalation techniques.

Antimuscarinics

Ipratropium bromide has been studied more extensively than any other antimuscarinic in asthmatic children. Although the importance of antimuscarinics in the treatment of asthma remains uncertain,[32] ipratropium can cause bronchodilation in some asthmatic children.[33,34] Administration of nebulized ipratropium at doses that ranged from 125-1,000 μg to asthmatic children 5-14 years of

age elicited mean increases in FEV_1 of 30-60% within 5 minutes, maintained for at least 90 minutes.[33] There were no adverse effects.

A randomized, double-blind, crossover study of responses to nebulized ipratropium bromide in asthmatic children 9-17 years of age disclosed dose-dependent bronchodilation that was significant at 75 μg, with a similar response to 250 μg.[34] Significant improvement in FEV_1 occurred within 15 minutes and peaked at 45 minutes. There were no side effects.

Addition of nebulized ipratropium to treatment with nebulized albuterol can elicit further improvement in children treated for acute asthma, at least when less than maximal doses of albuterol are used. In a randomized, double-blind, parallel group study of 25 children with acute asthma, both groups received nebulized albuterol, 0.15 mg/kg (maximum 5 mg) followed by 0.05 mg/kg (maximum 1.7 mg) at intervals of 20 minutes by nebulization for 2 hours.[35] At 60 minutes, ipratropium bromide, 250 μg, was also administered to one group. Improvement occurred in both groups, but addition of ipratropium elicited significantly greater improvement in FEV_1 within 60 minutes. There were no adverse effects except for tremor ascribed to albuterol.

Nebulized ipratropium, 250 μg, is also safe and effective in the treatment of acute airway obstruction in infants 3-32 months of age.[36] Specific conductance improved by more than 15% in 5 of 16 infants less than 13 months of age, with no adverse effects of ipratropium.

Cromolyn Sodium

Cromolyn sodium is available as a solution for nebulization (20 mg/2 mL), as an aerosol for delivery from an MDI (1 mg/actuation), and as a dry powder (20 mg/capsule) for inhalation from the Spinhaler. Experience with adults suggests equivalence of 20 mg delivered by Spinhaler and 2 mg delivered from MDI.[37]

A randomized, double-blind study in asthmatic children 9-14 years of age confirmed better protection against exercise-induced asthma from 20 mg by Spinhaler than from 1 mg by MDI.[38] The small dose by MDI afforded significantly less protection from the bronchoconstrictive effect of cycle-ergometer exercise 15 minutes and 2 hours after inhalation, and only the 20 mg by Spinhaler still afforded some protection 6 hours after treatment, as compared with placebo.

Availability of the nebulizer solution has extended this therapy to children too young to use the Spinhaler. Delivery of 20 mg 4 times each day to 2- to 7-year-old children by Bennett Twin-Jet nebulizer attached to a face mask and driven by a Maximyst compressor can elicit significant decreases in frequency and severity of acute asthma.[39]

Nevertheless, 25% or more of patients treated with cromolyn fail to improve. Study of serum concentrations of cromolyn determined by radioimmunoassay after inhalation of cromolyn powder suggests that inadequate inhalation technique may account for many of these failures.[40] Twenty-five children, 7-14 years of age, with chronic asthma received cromolyn powder, 20 mg 4 times each day, for 8 weeks. They were instructed to inhale the cromolyn after a forced expiration, to keep their lips attached tightly to the mouthpiece, to take a deep, forceful inspiration, and to hold the breath for 10 seconds afterwards. After 8 weeks of treatment, inhalation technique was evaluated and blood was sampled periodically after inhalation of cromolyn for determination of serum concentrations.

Serum cromolyn concentrations increased rapidly, peaking within 15 minutes and returned almost to baseline within 2 hours. Symptomatic improvement from the 2 weeks before initiation of treatment with cromolyn and improvement in mean peak expiratory flowrates measured twice daily correlated with peak cromolyn concentrations, concentration 10 minutes after inhalation, and the area under the cromolyn concentration time curve. There was also highly significant correlation between the pharmacokinetic variables and technique of inhalation, rated on a scale of 0 to 3 for strength and length of inhalation, motivation, and positioning of head and Spinhaler. Furthermore, peak cromolyn concentrations increased from a mean of 19 μg/L to 64 μg/L in 3 of 4 children with low peaks when inhalation was repeated after reinstruction in use of the inhaler.[40] Decreased inspiratory flowrate due to airway obstruction can also impair delivery of cromolyn to the lungs, in-

dicating the need for use of a bronchodilator before treatment with cromolyn in such patients, but the children in this study were not considered severely obstructed.

This observation of correlation of response to cromolyn with serum concentrations, which indicates extent of delivery to the lungs, provides a basis for use of doses larger than usual in patients with inadequate responses.[40]

Measurement of urinary cromolyn concentrations for 8 hours after inhalation of cromolyn in 9 children, 9-36 months of age, with frequently recurrent wheezing, suggests delivery of less than 1% of the administered aerosol to the lungs in this age group.[41] Cromolyn solution, 20 mg diluted to 4 mL with normal saline, was nebulized by an Acorn nebulizer driven by compressed air at 8 L/min and attached to a face mask. On a different day, the children received the same total dose from an MDI via a Medic Aid multispacer. Seven healthy adults also received cromolyn nebulized by the Acorn nebulizer with face mask and were instructed to use tidal nasal breathing from the face mask.

Cumulative urinary excretion of cromolyn was significantly greater after nebulization than after treatment with the spacer in the children and significantly greater in the adults than in the children after nebulization. Assuming cromolyn excretion in young children to be similar to that of adults, the authors calculated pulmonary absorption of only 0.76% of the nebulized cromolyn in the children and 0.30% of the dose delivered to the spacer. The very small proportion of the drug absorbed from the gastrointestinal tract also contributed to cromolyn excretion; accordingly, even less than these small calculated amounts actually reached the lungs.[41]

The spacer used had an output only 27% of that of the Nebuhaler, but its output exceeded flowrates generated by toddlers during tidal breathing.

The estimated pulmonary dose for one adult who breathed through the mouth rather than the nose was 4.4% of the nebulized dose, suggesting substantial loss of drug in the other subjects due to nasal filtration.[41]

Although the disparity between these calculated lung doses and those estimated by other methods remains to be explained, these data indicate delivery of less cromolyn to the lungs of infants than adults, suggesting a need for better methods of delivery or use of larger doses in infants.[15]

Nedocromil Sodium

There have been very few studies of nedocromil sodium in children, but inhalation of 4 mg via MDI 15 and 30 minutes before treadmill exercise in 7- to 15-year-old children has inhibited postexercise decreases in peak expiratory flowrate and FEV_1 significantly as compared with placebo in double-blind crossover studies.[42,43]

Inhaled Adrenal Corticosteroids

Numerous studies attest to the safety and efficacy of inhaled beclomethasone for the control of asthma in children 5-19 years of age at 300-400 μg daily in divided doses.[44-46] There has been improvement in symptoms and pulmonary function with lessening of need for other antiasthmatic medications, including oral adrenal corticosteroids in those who were steroid-dependent.

Bronchial responsiveness to inhaled methacholine decreased significantly during 6 months of treatment with inhaled budesonide, 200 μg 3 times daily, in 7 of 12 asthmatic children 7-16 years of age.[47] The greatest improvement occurred after the first month. No improvement occurred in 7 other children treated only with inhaled terbutaline, 500 μg 3 times each day.

Control of most symptoms of asthma and peak expiratory flowrate, measured twice daily, is not significantly different in children with mild asthma when the total daily dosage of 400 μg beclomethasone is divided into 2 rather than 4 doses.[48] Improved compliance with the twice-daily regimen and obviation of the need for administration of medication at school more than make up for a slightly increased tendency toward wheezing during the day.

A randomized, double-blind, placebo-controlled trial of large doses of inhaled beclomethasone, 750 μg 3 times daily for 5 days, failed to affect frequency of need for oral corticosteroids or admission to the hospital in 35 pairs of episodes of acute wheezing in 24 children 1-5 years of age.[49] The

beclomethasone was delivered from MDIs, 250 μg per actuation, via Volumatic spacers. There was a significant reduction in symptoms during the first week of the episode of wheezing with initiation of treatment with high-dose beclomethasone at the first sign of symptoms of acute asthma. Failure to observe more conclusive results may have been due to inability of the young children to open the valve of the spacer adequately during acute airway obstruction or to insufficient numbers of episodes for evaluation.

Nebulized beclomethasone is also effective in reducing symptoms in young asthmatic children. A double-blind, placebo-controlled, parallel study of 29 asthmatic children 1-5 years of age disclosed less frequent wheezing and less use of bronchodilators in those treated with nebulized beclomethasone, 100 μg 3 times daily, for 6 months.[50] The beclomethasone was delivered by face mask from an Acorn nebulizer. No adverse effects were evident. No corticosteroid suspension for nebulization is available yet in the United States.

Most studies of beclomethasone dipropionate aerosol in children have disclosed adequate control of asthma without evidence of adrenal suppression at recommended doses of 100 μg 3-4 times daily (maximal total daily dosage 500 μg).[44-46] However, some pituitary-adrenal suppression can occur at slightly larger doses and may occur in both children and adults when total daily dosage exceeds 14 μg/kg.[51,52]

Nocturnal, dose-dependent suppression of plasma cortisol concentrations is greater than daytime suppression in asthmatic children treated with inhaled beclomethasone.[53]

Despite the potential for pituitary-adrenal suppression, serious adverse effects of inhaled corticosteroids have been quite rare. Three children who died during or shortly after substitution of inhaled beclomethasone, 400 μg daily, for oral prednisolone, probably received insufficient doses of supplemental oral corticosteroids for their terminal episodes of acute asthma associated with tracheobronchitis.[54]

There has been a single report of truncal obesity, hirsutism, and suppression of linear growth, in an 8-year-old girl treated for asthma with inhaled triamcinolone acetonide aerosol, 300 μg twice daily, for 10 months.[55] There was associated suppression of serum cortisol concentrations and 24-hour urinary 17-hydroxycorticosteroid excretion. The obesity resolved, and a linear growth spurt followed discontinuation of triamcinolone.

Inhalation of triamcinolone acetonide aerosol at dosages of 100-300 μg 4 times daily has usually been safe and effective in asthmatic children.[56]

Flunisolide aerosol, 500 μg twice daily, is also safe and effective for control of asthma in children.[57] Administration by nebulization, 500 μg twice daily, is also safe and effective.[58]

Antiviral Agents

Ribavirin is the only antiviral agent available for nebulization. It is a synthetic nucleoside with in-vitro activity against a number of different viruses, including respiratory syncytial virus (RSV). It has been available for clinical use since 1985, but uncertainty about its efficacy and safety remains because of the few patients evaluated in controlled studies, reservations about comparability of active and placebo groups, uncertainties about the adequacy of clinical scoring systems employed, and the small, although significant, differences in clinical scores and oxygen saturation or transcutaneous oxygen tension observed.[59-61]

Published guidelines suggest consideration of use of ribavirin for treatment of RSV infections in infants at high risk of severe disease as a result of chronic lung conditions, congenital heart disease, or immunodeficiency; in infants severely ill, especially those with P_{aO_2} less than 65 torr or increasing carbon dioxide levels; and in infants less than 6 weeks of age.[62] Despite limitation of use of ribavirin to such infants at high risk of significant morbidity from RSV infection, ribavirin may be used in as many as half of infants admitted to tertiary care centers for treatment of suspected RSV infection.[63]

Administration of ribavirin is costly, cumbersome, and time-consuming. The drug is nebulized by a Viratek Small Particle Aerosol Generator (SPAG-2) for 12-18 hours per day for 3-7 days from a solution of 20 mg/mL and delivered to an infant oxygen hood. The generator produces particles with a mass median diameter of approximately 1.3 μm.

Nebulization of a more concentrated solution of 60 mg/mL for 2 hours 3 times each day for 3-5 days has been found feasible, safe, and effective in 9 infants and children.[64] This reduction in nebulization time increases accessibility of the patient for care and reduces environmental exposure of health-care providers.

Infants who require mechanical ventilation because of severe impairment due to RSV infection may be among those most in need of treatment, but the manufacturer recommends not using ribavirin in such patients because precipitation of drug in the equipment may increase positive end-expiratory pressure.[62] However, certain modifications that isolate the ventilator can permit continuous administration of aerosolized ribavirin to mechanically ventilated infants for as long as 7 days without ventilator malfunction.[65] Also, at least 12 infants who required mechanical ventilation for respiratory failure have been treated successfully with nebulized ribavirin by changing the circuit valves regularly at intervals of 4 hours and the tubing at intervals of 8 hours to prevent obstruction by precipitated drug.[66] Patients were also monitored closely for any possible adverse effect. Furthermore, a randomized, double-blind, placebo-controlled evaluation of aerosolized ribavirin in infants with severe RSV infection that necessitated mechanical ventilation disclosed significant shortening of the need for mechanical ventilation and supplemental oxygen and shortening of duration of hospitalization.[67]

Reports of adverse reactions to ribavirin from January 1986 through September 1988, forwarded to the manufacturer by the United States Department of Health and Human Services, indicated reported reactions at a rate of 0.09%.[68] The most common side effects were cutaneous eruptions and mild bronchospasm.

Retrospective review of charts of 577 patients treated with ribavirin at 8 hospitals disclosed improvement in 78%.[68] Initial bronchospasm necessitated discontinuation of the drug in one infant. There were 11 deaths, including 8 infants with severe bronchopulmonary dysplasia and 3 with complex cardiac defects, but no death was ascribed to treatment with ribavirin.

Respiratory therapists and nurses at 1 of 8 hospitals reviewed "commonly" complained of headache and excessive tearing while delivering ribavirin, but these adverse effects were mild and resolved with discontinuation of exposure to the drug.[68]

It is prudent for pregnant health-care workers to avoid exposure to ribavirin because teratogenicity has been found in pregnant rodents, although none has been found in pregnant baboons.[68]

Antibiotics

Aerosolization of antibiotics remains controversial because of expense and concerns about adequacy of delivery to infected segments of lung, emergence of resistant strains of organisms, and induction of hypersensitivity. There have been few controlled studies to address these concerns.

Lung scans after inhalation of radioaerosols delivered from a DeVilbiss #900 ultrasonic nebulizer to clinically stable children with cystic fibrosis confirm nonuniform deposition of aerosol, with diminished deposition in poorly ventilated regions as indicated by retention of xenon-133.[69] Deposition of radioaerosols delivered from a Centimist nebulizer at 9 L/min (mass median aerodynamic diameter 1.1 μm) in adults with cystic fibrosis depends upon minute ventilation and extent of airway obstruction.[70] As percent predicted FEV_1 decreased, the proportion of aerosol deposited in central airways increased. The amount of gentamicin deposited as determined by measurement in expectorated sputum was optimal at minute ventilations of approximately 8-15 L/min, and was reduced at both lower and higher minute ventilations.[70]

Despite these data indicating effects of pulmonary disease on aerosol deposition, concentrations of gentamicin in tracheobronchial secretions are higher 1 hour after administration by aerosol than after intramuscular injection.[71] Fourteen children, including 8 with cystic fibrosis and 6 with tracheostomies, were studied after administration of gentamicin, 40 mg, by aerosol or endotracheal instillation. Concentrations in tracheobronchial secretions exceeded 20 μg/mL in 7 children after aerosolization and in 11 after endotracheal instillation. Intramuscular injection of single doses of 1.5 mg/

kg resulted in concentrations less than 2 μg/mL in tracheobronchial secretions of 10 children, including 4 with undetectable levels.

Determination of serum gentamicin concentrations has disclosed dose-dependent absorption from the respiratory tracts of children with cystic fibrosis after nebulization of 120, 360, and 600 mg on different days.[72] Delivery was via mouthpiece from a jet nebulizer that produced particles 0.5-5.5 μm in size with output of 0.38 mL/min, and patients activated the nebulizer manually for each inspiration. Thus, administration by nebulization of larger than usual doses might achieve serum concentrations adequate for an antibacterial effect in poorly ventilated regions of lung with adequate perfusion.

There have been several reports of improvement in children with cystic fibrosis or other pulmonary diseases treated with aerosolized antibiotics[73-76] but no placebo-controlled studies.

A randomized comparison of intravenous ticarcillin (300 mg/kg/day) and tobramycin (10 mg/kg/day) for 2 weeks with the same intravenous treatment plus nebulized tobramycin (80 mg 3 times each day) disclosed similar significant improvement in clinical scores and pulmonary function in both groups, but temporary eradication of *Pseudomonas aeruginosa* in significantly more of the patients who received inhalation therapy (63% compared with 25%).[73]

Treatment with nebulized tobramycin 3 times daily for 12 weeks in 22 children, adolescents, and young adults with cystic fibrosis was associated with emergence of strains of *P aeruginosa* resistant to tobramycin in 73% of those with susceptible sputum isolates on admission to the study.[75] However, symptomatic improvement and reduction in sputum *P aeruginosa* density occurred during treatment, and 1 year later no isolates were resistant. Furthermore, the mean peak sputum tobramycin concentration of 2,300 μg/mL greatly exceeded the usual definition of resistance, which may require modification for antibiotics delivered by nebulization.

Treatment with nebulized tobramycin twice daily for 1-3 years in 14 children and adolescents with cystic fibrosis was associated with clinical improvement despite emergence of resistant strains of *P aeruginosa* in 5 patients after 10-21 months of treatment.[74] By the end of the study only one patient still harbored resistant organisms.

Administration by nebulization has not been reported to increase the frequency of induction of hypersensitivity to antibiotics, but this has not been evaluated fully.[25]

Mucolytic Agents

Although *n*-acetylcysteine can decrease the consistency of sputum in vitro by opening disulfide bonds in mucus,[77] clinical efficacy after administration by nebulization has not been established in controlled studies.

Pentamidine

Aerosolized pentamidine is effective for the treatment of pneumonia due to *Pneumocystis carinii* in adults, but published reports are limited to experience with adults. Young children probably are unable to cooperate sufficiently for effective prophylaxis or treatment with nebulized pentamidine. However, the Centers for Disease Control have recommended aerosolized pentamidine for children at least 5 years of age infected with human immunodeficiency virus and unable to tolerate trimethoprim-sulfamethoxazole.[78]

The dose recommended for adults, 300 mg every 4 weeks via the Respirgard II jet nebulizer, has also been used in children, although pharmacokinetic or efficacy data are unavailable in children. The dose is diluted in 6 mL sterile water and delivered at 6 L/min from a 50 psi compressed air source until the reservoir is dry.[79]

Adverse Effects of Aerosol Therapy

Adverse reactions to aerosols may be due to reaction to the drug itself, to propellants or preservatives, or to physical properties of the aerosol.[80]

Beta Agonists

Potentially adverse effects of beta agonists include aggravation of hypoxemia,[81] cardiac stimulation,[12,13,81] hypokalemia,[12,13,81] tolerance,[81] and ag-

gravation of bronchial hyperresponsiveness.[47,82] Changes in arterial P_{O_2} after inhalation of beta-agonist aerosols have been small, largest in patients with relatively high P_{O_2}, and transient.[81] Accordingly, their significance is minimal, but it is prudent to administer supplemental oxygen when treating severe airway obstruction with a beta agonist.

Cardiac stimulation, cardiac arrhythmias, and hypokalemia are less important potential adverse effects in children than in adults and less likely with aerosol therapy than with systemic therapy.[81] Nevertheless, it is prudent to monitor cardiac activity and serum potassium concentrations when administering frequent, large doses of beta agonist by aerosol.[12,13]

Tolerance, subsensitivity, or decreased responsiveness to beta agonists after continual treatment for at least 2 weeks has been found by some investigators mostly in adults, but not by others.[81] Tolerance to oral beta agonists has been reported in children.[83] The modest losses of responsiveness observed might be compensated for by increased dosage, and concurrent treatment with corticosteroids may minimize tolerance.[84]

Association of increased bronchial hyperresponsiveness with continual treatment with beta agonists is of greater concern.[82] A modest but significant increase in bronchial hyperresponsiveness to methacholine occurred within the first month of treatment with inhaled terbutaline, 500 μg 3 times daily in 7 children with mild asthma.[47] This was associated with no increase in symptoms or worsening of pulmonary function during 6 months of treatment.

A double-blind, crossover, placebo-controlled study of inhalation of fenoterol powder (200 μg 4 times each day for 24 weeks in asthmatic adolescents and adults) disclosed more than a two-fold increase in bronchial hyperresponsiveness to methacholine in 22 of 64 patients during continual treatment with fenoterol as compared with the 24 weeks during which they received placebo and used inhaled beta agonist (fenoterol, albuterol, or terbutaline) only when needed for relief of symptoms.[82] Significantly better symptomatic control occurred during intermittent use of beta agonists than during continual treatment with fenoterol. Fifty of the 64 patients were receiving concurrent treatment with inhaled corticosteroids. The extent to which these observations with fenoterol can be generalized to other beta agonists is unknown.

Corticosteroids

Inhaled corticosteroids can cause oropharyngeal candidiasis, reduced total body calcium, adrenal suppression, and possibly posterior, subcapsular cataracts.[85] Candidiasis rarely necessitates discontinuation of treatment and can be prevented by use of a spacer.[86] Adrenal suppression may occur in some asthmatic children treated with inhaled beclomethasone at doses that exceed 14 μg/kg/day or 400 $\mu g/m^2$/day.[51,52,87]

Propellants

Fluorocarbon propellants in MDIs are not likely to elicit adverse cardiac effects, although they can cause cardiac arrhythmias in anesthetized, hypoxic mice.[88] Concurrent administration of inhaled fluorocarbons and intravenous isoproterenol at doses equivalent to 300 actuations of a MDI (80 μg per actuation) has failed to cause arrhythmias in hypoxic dogs.[89] Continual administration of propellant with or without isoproterenol or albuterol (one inhalation with each of 40 successive inspirations without permitting access to air) has caused convulsions in dogs, but all except two that received isoproterenol recovered.[90]

It has been estimated that one actuation of a MDI with each of 12-24 successive breaths would be necessary to achieve blood and myocardial concentrations in humans such as those that have sensitized dogs to toxic effects of epinephrine.[91]

Preservatives

Most commercially available nebulizer solutions contain preservatives (Table 1). Preservatives that can cause bronchoconstriction in some asthmatic patients include sulfites,[92] benzalkonium chloride,[93,94] ethylene diamine tetra-acetic acid (EDTA),[94] and chlorbutol.[95] The bronchodilating activity of beta-agonist aerosols is probably usually more than adequate to overcome the bronchoconstrictive action of preservatives present, and 0.5

Table 1. Characteristics of Nebulizer Solutions

Drug	Trade Name	pH	Osmolality (mOsm/kg)	Preservatives
Albuterol	Proventil	3.0-5.0	—	BKC* 0.01%
	Ventolin 0.5%		230†, 38‡	—
	Proventil 0.083%	3.0-5.0	—	BKC 0.01%
Metaproterenol	Alupent 5%	2.8-3.5	274§	BKC 0.025%
Terbutaline	Brethine Bricanyl	3.0-5.0	Isotonic	None
Cromolyn sodium	Intal	4.0-7.0	42	None
n-acetylcysteine	Mucomyst 10%	6.5-7.5	1.4	EDTA 0.25 g/L
	Mucomyst 20%	6.5-7.5	3.1	EDTA 0.5 g/L
Ribavirin	Virazole	5.0-6.9	79	None

* BKC = benzalkonium chloride; EDTA = ethylene diamine tetra-acetic acid.
† After dilution with 2 mL normal saline.
‡ After dilution with 2 mL cromolyn sodium nebulizer solution.
§ After dilution with 2.2 mL normal saline.

mL of the 0.5% albuterol solution contains only 50 μg benzalkonium chloride if diluted with preservative-free saline, less than the amount known to cause bronchoconstriction in some asthmatic patients.[93] Frequent administration of large doses, however, might elicit bronchoconstriction or less than optimal bronchodilation due to the preservative. Furthermore, although the concentration of benzalkonium chloride is the same in both preparations of albuterol solution, the 2.5-mg unit dose of the 0.083% solution contains 300-μg benzalkonium chloride, a dose that exceeds that to which 3 of 28 unselected asthmatic patients responded with bronchoconstriction.[93]

It is unknown to what extent the bronchoconstriction commonly elicited by *n*-acetylcysteine in asthmatic patients may be due to the preservative, the hypotonicity of the solution, or irritating properties of the drug, but the response is so common that many consider the drug contraindicated in patients with asthma.

Physical Properties

Inhalation of aerosols of either hypotonic or hypertonic solutions can cause bronchoconstriction in patients with asthma.[96] The clinical relevance of osmolality of aerosol solutions is emphasized by observations that isotonic solutions of cromolyn sodium afford better protection against the bronchoconstrictive effects of exercise[97,98] and inhalation of methacholine[97] than does the commercially available hypotonic solution. Effects of hypotonicity on bronchodilator aerosols are less easy to evaluate, but extremely hypotonic solutions of beta agonists for aerosolization may afford less protection against exercise-induced asthma than only slightly hypotonic solutions in occasional asthmatic patients.[99] Albuterol diluted with 2 mL normal saline may occasionally afford better protection than albuterol diluted in cromolyn.

Osmolality of nebulizer solutions increases during nebulization, but cromolyn remains quite hypotonic after 15 minutes of nebulization.[100]

The bronchoconstrictive potential of acidic aerosols depends more on total available hydrogen ion concentration than pH alone, and acidic aerosols composed of respirable particles with mass median aerodynamic diameters < 6 μm may be more likely to provoke bronchoconstriction in asthmatic subjects than those composed of larger particles.[101] Although aerosols of solutions at pH 2 have only a

modest bronchoconstrictive effect, they can potentiate the bronchoconstrictive effect of hypo-osmolar aerosols.[102]

Conclusions

Aerosolized beta agonists, ipratropium bromide, cromolyn, and adrenal corticosteroids are of established efficacy in infants and children. Some antibiotic aerosols are probably effective, at least in patients with cystic fibrosis. Both antiasthmatic aerosols and antibiotic aerosols are safer than available alternative therapy.

- Ribavirin is probably effective in the treatment of RSV infection, and may be effective for milder disease.
- Mucolytic aerosols probably are not effective and may be dangerous in patients with asthma.
- Optimal, safe doses of most aerosols have not been established for infants and children, and there are urgent needs for better delivery systems for infants and young children.
- Potential effects of preservatives and physical properties of aerosols are poorly understood, but we should encourage manufacturers to market aerosols with preservatives and properties that are not likely to have adverse effects.
- The importance of aerosol therapy and limited knowledge of it suggest innumerable lines of possible research.

ACKNOWLEDGMENTS

I am grateful to the staffs of Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Institutional Products, Fisons Corporation, Glaxo Inc, ICN Pharmaceuticals Inc, and Schering Corporation for providing details about physical properties and preservatives in their products.

REFERENCES

1. Sly RM. Unlabeled use of approved drugs. J Allergy Clin Immunol 1983;71:515-517.
2. Ellis EF. Asthma: current therapeutic approach. Pediatr Clin North Am 1988;35:1041-1052.
3. Mellis CM. Important changes in the emergency management of acute asthma in children. Med J Aust 1988;148:215-217.
4. Richards W. Hospitalization of children with status asthmaticus: a review. Pediatrics 1989;84:111-118.
5. Newcomb RW. Use of adrenergic bronchodilators by pediatric allergists and pulmonologists. AJDC 1989; 143:481-485.
6. Canny GJ, Levison H. Childhood asthma: a rational approach to treatment. Ann Allergy 1990;64:406-418.
7. British Thoracic Society. Guidelines for management of asthma in adults: II—acute severe asthma. Br Med J 1990;301:797-800.
8. Schwartz AL, Lipton JM, Warburton D, Johnson LB, Twarog FJ. Management of acute asthma in childhood. AJDC 1980;134:474-478.
9. Ben-Zvi Z, Lam C, Hoffman J, Teets-Grimm KC, Kattan M. An evaluation of the initial treatment of acute asthma. Pediatrics 1982;70:348-353.
10. Becker AB, Nelson NA, Simons FER. Inhaled salbutamol (albuterol) vs injected epinephrine in the treatment of acute asthma in children. J Pediatr 1983;102: 465-469.
11. Robertson CF, Smith F, Beck R, Levison H. Response to frequent low doses of nebulized salbutamol in acute asthma. J Pediatr 1985;106:672-674.
12. Schuh S, Parkin P, Rajan A, Canny G, Healy R, Rieder M, et al. High- versus low-dose, frequently administered, nebulized albuterol in children with severe, acute asthma. Pediatrics 1989;83:513-518.
13. Schuh S, Reider MJ, Canny G, Pender E, Forbes T, Tan YK, et al. Nebulized albuterol in acute childhood asthma: comparison of two doses. Pediatrics 1990;86:509-513.
14. Portnoy J, Aggarwal J. Continuous terbutaline nebulization for the treatment of severe exacerbations of asthma in children. Ann Allergy 1988;60:368-371.
15. Moler FW, Hurwitz ME, Custer JR. Improvement in clinical asthma score and P_{aCO_2} in children with severe asthma treated with continuously nebulized terbutaline. J Allergy Clin Immunol 1988;81:1101-1109.
16. Voss KR, Willsie-Ediger SK, Pyszczynski DR, Nelson KA. Description of a delivery method for continuously aerosolized albuterol in status asthmaticus. J Asthma 1990;27:37-39.
17. Ritchie D, Erban A, McLennan L, Landau LI, Phelan PD. Doses of terbutaline respirator solution in children with asthma. NZ Med J 1979;90:332-334.
18. Bentur L, Kerem E, Canny G, Reisman J, Schuh S, Stein R, et al. Response of acute asthma to a $beta_2$ agonist in children less than two years of age. Ann Allergy 1990;65:122-126.
19. Littner MR, Tashkin DP, Siegel SC, Katz R. Double-blind comparison of acute effects of inhaled albuterol, isoproterenol and placebo on cardiopulmonary function and gas exchange in asthmatic children. Ann Allergy 1983;50:309-316.
20. Berkowitz R, Schwartz E, Bukstein D, Grumstein M, Chai H. Albuterol protects against exercise-induced asthma longer than metaproterenol sulfate. Pediatrics 1986;77:173-178.

21. Sly RM, Heimlich EM, Ginsburg J, Busser RJ, Strick L. Exercise-induced bronchospasm: evaluation of metaproterenol. Ann Allergy 1968;26:253-258.
22. Lee H, Evans HE. Evaluation of inhalation aids of metered dose inhalers in asthmatic children. Chest 1987; 91:366-369.
23. Rachelefsky GS, Rohr AS, Wo J, Gracey V, Spector SL, Siegel SC, et al. Use of a tube spacer to improve the efficacy of a metered-dose inhaler in asthmatic children. AJDC 1986;140:1191-1193.
24. Hodges IGC, Milner AD, Stokes GM. Assessment of a new device for delivering aerosol drugs to asthmatic children. Arch Dis Child 1981;56:787-800.
25. Sly RM, Barbera JM, Middleton HB, Eby DM. Delivery of albuterol aerosol by Aerochamber to young children. Ann Allergy 1988;60:403-406.
26. O'Callaghan C, Milner AD, Swarbrick A. Spacer device with face mask attachment for giving bronchodilators to infants with asthma. Br Med J 1989;298:160-161.
27. Rivlin J, Mindorff C, Reilly P, Levison H. Pulmonary response to a bronchodilator delivered from three inhalation devices. J Pediatr 1984;104:470-473.
28. Fuglsang G, Pedersen S. Comparison of Nebuhaler and nebulizer treatment of acute severe asthma in children. Eur J Respir Dis 1986;69:109-113.
29. Pedersen S. How to use a Rotahaler. Arch Dis Child 1986;61:11-14.
30. Hansen OR, Pedersen S. Optimal inhalation technique with terbutaline Turbuhaler. Eur Respir J 1989;2:637-639.
31. Hultquist C, Ahlstrom H, Kjellman N-IM, Malmqvist L-A, Svenonius E, Melin S. A double-blind comparison between a new multidose powder inhaler (Turbuhaler) and metered dose inhaler in children with asthma. Allergy 1989;44:467-470.
32. Weber RW. Role of anticholinergics in asthma. Ann Allergy 1990;65:348-350.
33. Lenney W, Evans NAP. Nebulized salbutamol and ipratropium bromide in asthmatic children. Br J Dis Chest 1986;80:59-65.
34. Davis A, Vickerson F, Worsley G, Mindorff C, Kazim F, Levison H. Determination of dose-response relationship for nebulized ipratropium in asthmatic children. J Pediatr 1984;105:1002-1005.
35. Beck R, Robertson C, Galdes-Sebaldt M, Levison H. Combined salbutamol and ipratropium bromide by inhalation in the treatment of severe acute asthma. J Pediatr 1985;107:605-608.
36. Hodges IGC, Groggins RC, Milner AD, Stokes GM. Bronchodilator effect of inhaled ipratropium bromide in wheezy toddlers. Arch Dis Child 1981;56:729-732.
37. Lal S, Malhotra SM, Gribben MD. Comparison of sodium cromoglycate pressurized aerosol and powder in the treatment of asthma. Clin Allergy 1982;12:197-201.
38. Bar-Yishay E, Gur I, Levy M, Volozni D, Godfrey S. Duration of action of sodium cromoglycate on exercise induced asthma: comparison of 2 formulations. Arch Dis Child 1983;58:624-627.
39. Hilman BC, Bairnsfather L, Washburne W, Vekovius AL. Nebulized cromolyn sodium: safety, efficacy, and role in the management of childhood asthma. Pediatr Asthma Allergy Immunol 1987;1:43-52.
40. Yahav Y, Dany S, Katznelson D, Farfel Z. Sodium cromoglycate in asthma: correlation between response and serum concentrations. Arch Dis Child 1988;63:592-597.
41. Salmon B, Wilson NM, Silverman M. How much aerosol reaches the lungs of wheezy infants and toddlers? Arch Dis Child 1990;65:401-403.
42. Henriksen JM. Effect of nedocromil sodium on exercise-induced bronchoconstriction in children. Allergy 1988;43:449-453.
43. Boner AL, Vallone G, Bennati D. Nedocromil sodium in exercise-induced bronchoconstriction in children. Ann Allergy 1989;62:38-41.
44. Francis RS. Long-term beclomethasone dipropionate aerosol therapy in juvenile asthma. Thorax 1976; 31:309-314.
45. Klein R, Waldman D, Kershnar H, Berger W, Coulson A, Katz R, et al. Treatment of chronic childhood asthma with beclomethasone dipropionate aerosol: I. A double-blind crossover trial in nonsteroid-dependent patients. Pediatrics 1977;60:7-13.
46. Kershnar H, Klein R, Waldman D, Berger W, Rachelefsky G, Katz R, et al. Treatment of chronic childhood asthma with beclomethasone dipropionate aerosols: II. Effect on pituitary-adrenal function after substitution for oral corticosteroids. Pediatrics 1978;62:189-197.
47. Kerrebijn KF, van Essen-Zandvliet EEM, Neijens HJ. Effect of long-term treatment with inhaled corticosteroids and beta-agonists on the bronchial responsiveness in children with asthma. J Allergy Clin Immunol 1987;79:653-659.
48. Williams H, Jones ERV, Sibert JR. Twice daily versus four times daily treatment with beclomethasone dipropionate in the control of mild childhood asthma. Thorax 1986;41:602-605.
49. Wilson NM, Silverman M. Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. Arch Dis Child 1990; 65:407-410.
50. Storr J, Lenney CA, Lenney W. Nebulised beclomethasone dipropionate in preschool asthma. Arch Dis Child 1986;61:270-273.
51. Wyatt R, Wascher J, Weinberger M, Sherman B. Effects of inhaled beclomethasone dipropionate and alternate-day prednisone on pituitary-adrenal function in children with chronic asthma. N Engl J Med 1978;299:1387-1392.
52. Sherman B, Weinberger M, Chen-Walden H, Wendt H. Further studies of the effects of inhaled glucocorticoids on pituitary-adrenal function in healthy adults. J Allergy Clin Immunol 1982;69:208-212.
53. Law CM, Marchant JL, Honour JW, Preece MA, Warner JO. Nocturnal adrenal suppression in asthmatic children taking inhaled beclomethasone dipropionate. Lancet 1986;1:942-944.

54. Mellis CM, Steiner N, Phelan PD. Beclomethasone dipropionate aerosol for asthmatic children requiring maintenance oral steroid therapy. Med J Aust 1976; 1:957-962.
55. Hollman GA, Allen DB. Overt glucocorticoid excess due to inhaled corticosteroid therapy. Pediatrics 1988; 81:452-455.
56. Sly RM, Imseis M, Frazer M, Joseph F. Treatment of asthma in children with triamcinolone acetonide aerosol. J Allergy Clin Immunol 1978;62:76-82.
57. Meltzer EO, Kemp JP, Orgel A, Izu AE. Flunisolide aerosol for treatment of severe, chronic asthma in steroid-independent children. Pediatrics 1982;69:340-345.
58. Piacentini GL, Sette L, Peroni DG, Bonizzato C, Bonetti S, Boner AL. Double-blind evaluation of effectiveness and safety of flunisolide aerosol for treatment of bronchial asthma in children. Allergy 1990;45:612-616.
59. Rodriguez WJ, Kim HW, Brandt CD, Fink RJ, Getson PR, Arrobio J, et al. Aerosolized ribavirin in the treatment of patients with respiratory syncytial virus disease. Pediatr Infect Dis J 1987;6:159-163.
60. Wald ER, Dashefsky B, Green M. In re ribavirin: a case of premature adjudication? J Pediatrics 1988;112:154-158.
61. Milner AD. Ribavirin and acute bronchiolitis in infancy. Br Med J 1988;297:998-999.
62. Committee on Infectious Diseases. Ribavirin therapy of respiratory syncytial virus. Pediatrics 1987;79:475-478.
63. Herzog KD, Long SS, McGuigan M, Fisher MC, Deforest A. Impact of treatment guidelines on use of ribavirin. AJDC 1990;144:1001-1004.
64. Englund JA, Piedra PA, Jefferson LS, Wison SZ, Taber LH, Gilbert BE. High-dose, short-duration ribavirin aerosol therapy in children with suspected respiratory syncytial virus infection. J Pediatr 1990;117:313-320.
65. Demers RR, Parker J, Frankel LR, Smith DW. Administration of ribavirin to neonatal and pediatric patients during mechanical ventilation. Respir Care 1986; 31:1188-1195.
66. Outwater KM, Meissner HC, Peterson MB. Ribavirin administration to infants receiving mechanical ventilation. AJDC 1988;142:512-515.
67. Smith DW, Frankel LR, Mathers LH, Tang ATS, Ariagno RL, Prober, CG. A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytrial virus infection. N Engl J Med 1991;325:24-29.
68. Janai HK, Marks MI, Zaleska M, Stutman HR. Ribavirin: adverse drug reactions, 1986 to 1988. Pediatr Infect Dis J 1990;9:209-211.
69. Alderson PO, Secker-Walker RH, Strominger DB, Markham J, Hill RL. Pulmonary deposition of aerosols in children with cystic fibrosis. J Pediatr 1974;84:479-484.
70. Howite JS, Gorvoy JD, Smaldone GC. Quantitative deposition of aerosolized gentamicin in cystic fibrosis. Am Rev Respir Dis 1987;136:1445-1449.
71. Baran D, Dachy A, Klastersky J. Concentration of gentamicin in bronchial secretions of children with cystic fibrosis or tracheostomy. Int J Clin Pharmacol Biopharm 1975;12:336-341.
72. Zach MS. Antibiotic treatment: aerosol therapy: discussion. Chest 1988;94(2, Suppl):160S-161S.
74. Stephens D, Garey N, Isles A, Levison H, Gold R. Efficacy of inhaled tobramycin in the treatment of pulmonary exacerbations in children with cystic fibrosis. Pediatr Infect Dis J 1983;2:209-211.
74. Steinkamp G, Tummler B, Gappa M, Albus A, Potel J, Doring G, et al. Long-term tobramycin aerosol therapy in cystic fibrosis. Pediatr Pulmonol 1989;6:91-98.
75. Smith AL, Ramsey BW, Hedges DL, Hack B, Williams-Warren K, Weber A, et al. Safety of aerosol tobramycin administration for 3 months to patients with cystic fibrosis. Pediatr Pulmonol 1989;7:265-271.
76. Weathers L, Riggs D, Santeiro M, Weibley RE. Aerosolized vancomycin for treatment of airway colonization by methicillin-resistant *Staphylococcus aureus*. Pediatr Infect Dis J 1990;9:220-221.
77. Sheffner AL, Medler EM, Jacobs LW, Sarett HP. The in vitro reduction in viscosity of human tracheobronchial secretions by acetylcysteine. Am Rev Respir Dis 1964; 90:721-729.
78. Centers for Disease Control. Guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for children infected with human immunodeficiency virus. MMWR 1991;40(RR-2):1-3.
79. Centers for Disease Control. Guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for persons infected with human immunodeficiency virus. MMWR 1989;38(S-5):1-9.
80. Snell NJC. Adverse reactions to inhaled drugs. Respir Med 1990;84:345-348.
81. Sly RM, Anderson JA, Bierman CW, Chervinsky P, Cogen FC, Easton JG, et al. Adverse effects and complications of treatment with beta-adrenergic agonist drugs. J Allergy Clin Immunol 1985;75:443-449.
82. Sears MR, Taylor DR, Print CG, Lake DC, Li Q, Fannery EM, et al. Regular inhaled beta-agonist treatment in bronchial asthma. Lancet 1990;336:1391-1396.
83. Nelson HS, Raine D Jr, Doner HC, Posey WC. Subsensitivity to the bronchodilator action of albuterol produced by chronic administration. Am Rev Respir Dis 1977;116:871-878.
84. Weber RW, Smith JA, Nelson HS. Aerosolized terbutaline in asthmatics: development of subsensitivity with long-term administration. J Allergy Clin Immunol 1982;70:417-422.
85. Kewley GD. Possible association between beclomethasone dipropionate aerosol and cataracts. Aust Paediatr J 1980;16:117-118.
86. Toogood JH, Baskerville J, Jennings B, Lefcoe NM, Johansson S-A. Use of spacers to facilitate inhaled corticosteroid treatment of asthma. Am Rev Respir Dis 1984;129:723-729.

87. Priftis K, Milner AD, Conway E, Honour JW. Adrenal function in asthma. Arch Dis Child 1990;65:838-840.
88. Taylor GJ, Harris WS. Cardiac toxicity of aerosol propellants. JAMA 1970;214:81-85.
89. Clark DG, Tinston DJ. Cardiac effects of isoproterenol, hypoxia, hypercapnia, and fluorocarbon propellants and their use in asthma inhalers. Ann Allergy 1972;30:536-541.
90. Jack D. Sniffing syndrome. Br Med J 1971;2:708-709.
91. Dollery CT, Williams FM, Draffan GH, Wise G, Sahyoun H, Paterson JW, et al. Arterial blood levels of fluorocarbons in asthmatic patients following use of pressurized aerosols. Clin Pharmacol Ther 1974;15:59-66.
92. Wright W, Zhang YG, Salome CM, Woolcock AJ. Effect of preservatives on asthmatic subjects: I. Sodium metabisulfite. Am Rev Respir Dis 1990;141:1400-1404.
93. Zhang YG, Wright WJ, Tam WK, Nguyen-Dang TH, Salome CM, Woolcock AJ. Effect of inhaled preservatives on asthmatic subjects: II. Benzalkonium chloride. Am Rev Respir Dis 1990;141:1405-1408.
94. Beasley CRW, Rafferty P, Holgate ST. Bronchoconstrictor properties of preservatives in ipratropium bromide (Atrovent) nebuliser solution. Br Med J 1987; 294:1197-1198.
95. Windom H, Burgess C, Crane J, Beasley R. The airways effects of inhaled chlorbutol in asthmatic subjects. Thorax 1990;45:343.
96. Eschenbacher WL, Boushey HA, Sheppard D. Alteration in osmolarity of inhaled aerosols causes bronchoconstriction and cough, but absence of a permeant anion causes cough alone. Am Rev Respir Dis 1984;129:211-215.
97. Weiner P, Saaid M, Reshef A. Isotonic nebulized disodium cromoglycate provides better protection against methacholine- and exercise-induced bronchoconstriction. Am Rev Respir Dis 1988;137:1309-1311.
98. Soferman R, Kivity S, Marcus B, Topilsky M. Comparison between bronchial response to inhaled hypoosmolar and isoosmolar solutions of sodium cromoglycate after exercise challenge. Ann Allergy 1990;64:143-146.
99. Soferman R, Kivity S, Topilsky M. The effect of osmolarity of respiratory salbutamol solutions on exercise-induced asthma in children. Pediatr Asthma Allergy Immunol 1990;4:193-198.
100. Schoni MH, Kraemer R. Osmolality changes in nebulizer solutions. Eur Respir J 1989;2:887-892.
101. Fine JM, Gordon T, Thompson JE, Sheppard D. The role of titratable acidity in acid aerosol-induced bronchoconstriction. Am Rev Respir Dis 1987;135:826-830.
102. Balmes JR, Fine JM, Christian D, Gordon T, Sheppard D. Acidity potentiates bronchoconstriction induced by hypoosmolar aerosols. Am Rev Respir Dis 1988;138: 35-39.

Aerosol Exhaust: Escape of Aerosolized Medication into the Patient and Caregiver's Environment

Robert J Fallat MD and Kathryn Kandal RRT

Introduction

Aerosol use in medicine is rapidly expanding. Asthma and chronic obstructive disease are now frequently treated solely with aerosols of beta stimulators, parasympatholytics, and steroids and other immune suppressors. Delivery of antibiotics via aerosol is being reconsidered. In the past few years, most concern has arisen over the use of two new aerosols because of their potential toxicity: pentamidine for the prevention and treatment of *Pneumocystis carinii* pneumonia (PCP) and ribavirin for the treatment of respiratory syncytial virus (RSV) infections.

Toxicity of all the aerosolized drugs is well recognized in the patient, but the potential toxicity of the lesser exposure to the caregiver is only beginning to be explored. It has been suggested that asthma occurring in respiratory therapists is related to their exposure to beta agonists,[1] and allergic responses to even small doses of aerosolized antibiotics may be possible. Ribavirin has known teratogenic activity in some species, and is aerosolized in a small particle size (1.3 μm) in order to penetrate deep into the lung;[2] this results in an aerosol difficult to contain and to adequately protect the health-care worker. Pentamidine is also aerosolized in a < 5 μm particle size, not only to provide deep penetration into the lung but also to minimize upper-airway irritation, which causes bronchospasm and cough: the patient's cough further endangers the health-care worker.

In this paper, we first discuss the evidence for the pulmonary toxicity of pentamidine in the health-care worker. (Dr Waskin will address the systemic toxicity of pentamidine and other agents in another paper in this issue.[3]) We then explore the possible ways to minimize the exposure of the health-care worker to potential toxicity by examining (1) the methods of delivery of aerosols, (2) control of the environment, and (3) direct protection of the health-care worker.

Pentamidine Toxicity

Acute airway reactions to pentamidine aerosol are common, easily recognized, and usually not major. A bitter or metallic taste, with some throat irritation, is the rule with the currently used doses. Bronchospasm and cough can probably be produced by pentamidine aerosol in everyone if given in high doses via standard nebulizers. We began prophylactic use of pentamidine aerosol in November, 1986, using 30 mg of pentamidine in 3 cc of water in a standard jet nebulizer, and with an exhaust filter. Mean particle size was 4-8 μm (Table 1), but particles >5 μm in size were not baffled and were therefore deposited in the patient's upper airway, causing cough and bronchospasm. All 29 patients studied showed some drop in $FEF_{25-75\%}$; 26 of the 29 had some decrease in FEV_1, but only 5 had >10% drop in FEV_1.[4] The use of albuterol aerosol prior to treatment prevented or minimized both cough and bronchospasm.

It was subsequently shown by Leoung et al that 300 mg (or 4 mg/kg of body weight) of pentamidine aerosol monthly was needed for effective prophylaxis,[5,6] and that 600 mg daily for 14-21 days was

Dr Fallat is Chief, Division of Pulmonary Medicine, and Ms Kandal is Research Coordinator, Respiratory Care Services—Pacific Presbyterian Medical Center, San Francisco, California.

A version of this paper was presented by Dr Fallat at the Consensus Conference on Aerosol Delivery, sponsored by the American Association for Respiratory Care, The American Respiratory Care Foundation, and the journal RESPIRATORY CARE, January 10-12, 1991, in Cancun, Mexico.

Reprints: Robert J Fallat MD, Division of Pulmonary Medicine, Pacific Presbyterian Medical Center, PO Box 7999, San Francisco CA 94120.

possibly effective for treatment of PCP.[5-7] In order to deliver these doses, Montgomery et al, in conjunction with Marquest Corporation, developed a specialized system, the Respirgard nebulizer[8] (Fig. 1). The nebulizer is specially designed internally to block the larger aerosol particles; in addition, one-way valves further reduce the mean particle size delivered to the patient. An exhaust filter is also used, which we will discuss later.

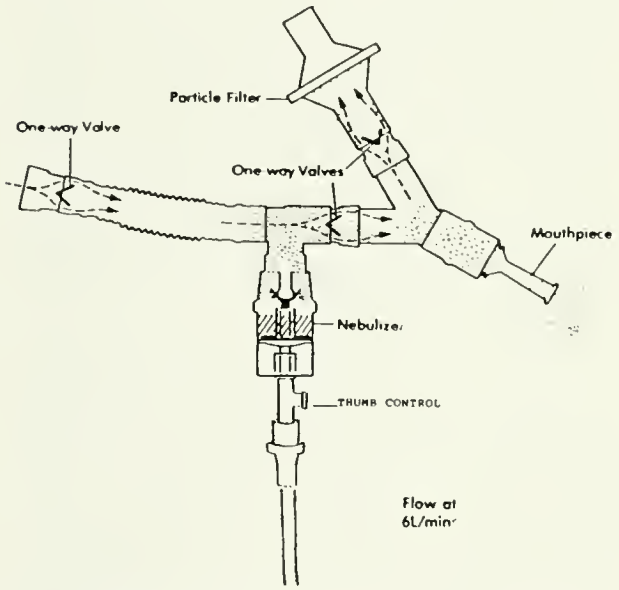


Fig. 1. Baffled nebulizing system used for delivery of pentamidine aerosol in the Respirgard II nebulizing system. One-way valves reduce the number of large particles delivered to the patient. The thumb control is not standard, but its use would allow the driving gas to bypass the nebulizer if not occluded during cough or rest periods, thus obviating discharge of aerosol into the atmosphere at such times.

With the Respirgard system, delivery of 300 mg of pentamidine aerosol still produced cough in 38% and bronchospasm in 15% of patients.[5] A decrease in FEV_1 of > 200 mL occurred in 56%, and a > 10% drop in FEV_1 in 32%.[9] A more sensitive index of bronchoconstriction, the airway resistance measured by body plethymography, has been shown to increase in all subjects receiving 600-mg pentamidine aerosol.[10] Almost all of the reduction in flows can be reversed or prevented with beta-agonist aerosol treatment, but some cough can be expected in 43-66% of patients receiving 300 mg of pentamidine aerosol,[4] and in up to 80% of those receiving 600 mg.[7] This not only introduces the patient's cough aerosol into the environment, but it may also result in pentamidine-aerosol escape unless a specialized system is used that automatically stops the aerosol when the nebulizing device is removed from the mouth.

The existence of long-term pulmonary toxicity of pentamidine aerosol has not been established. Debs et al[11] reported no histologic abnormalities in lungs, liver, or kidneys in mice after 14 daily doses of aerosolized pentamidine of 5.0 and 50.0 mg/kg of body weight. An increase in upper-lobe PCP with associated cystic changes[12] and pneumothoraces[13] following pentamidine aerosol prophylaxis has been described and was most likely due to the inadequate control of PCP in the apex caused by the poor distribution of pentamidine aerosol to that region. Of the 21 pneumothoraces seen in one clinical trial of 408 subjects,[5] only one was not associated with PCP or other causes of pneumothorax, and there was no correlation with the concentration of aerosol.

No significant changes were seen in lung volumes, flows, or diffusing capacity in 23 subjects followed for 143-531 days (median 371 days) after starting monthly 300-mg pentamidine aerosol prophylaxis.[9] On the other hand, there is an anecdotal report of a pulmonary function technician who, after 14 months of occupational exposure to pentamidine aerosol, was found to have a decrease in single-breath carbon monoxide diffusing capacity from 36 to 26 $mL \cdot torr \cdot min^{-1}$ (81% of the predicted value), which improved to 31 $mL \cdot torr \cdot min^{-1}$ after 9 days without exposure to the aerosol.[14] No adverse symptoms or other pulmonary-function abnormalities were present to suggest pulmonary or systemic toxicity. Many factors can affect the diffusing capacity measurement; further observations of health-care workers with long-term daily exposure to pentamidine are clearly needed. A detailed study of respiratory therapists working in five pentamidine aerosol clinics in San Francisco is now being carried out. The study includes longitudinal pulmonary function tests and methacholine challenge to look for potential parenchymal or airway toxicity from pentamidine. It is of interest that in one study there was no increase in hyperreactivity as measured with methacholine in 8 patients receiving 4 mg/kg of body weight of pentamidine aerosol monthly for 10-14 months.[15]

Because generally only 5-10% of the aerosolized pentamidine dose is delivered to the lungs, where it has a long retention time, and because there is no absorption from the gastrointestinal tract, systemic toxicity from pentamidine aerosol is rare, even in patients receiving 600 mg/day.[5,7] However, hypoglycemia and pancreatitis have been reported,[5,9] and questions of teratogenicity and carcinogenicity have not been resolved; these issues are discussed by Waskin.[3]

Methods of Aerosol Delivery and Environmental Contamination

Several methods of aerosol generation currently used and the characteristics and amounts of their aerosol output are summarized in Table 1. The range of particle sizes and outputs is wide. The potential for environmental contamination by the aerosol is greatest with ultrasonic nebulizers, which have a high output and can generate large particles. Baffled nebulizers have low output and small particle size, but the time needed for delivery of the dose is long, so the potential for leaks may increase.

Table 1. Characteristics of Aerosol from Several Types of Devices

Type of Device	MMAD* (μm)	Maximum Output (mL/min)
MDI	2-5	—
Rotahaler	2.6	—
Jet nebulizer	4-8	1.0-2.0
Baffled jet nebulizer	0.25-4.0	0.5-1.0
Ultrasonic nebulizer	1.60-6.0	6.0

*MMAD = mean mass aerodynamic diameter.

Metered dose inhalers (MDI) have the least potential for aerosol contamination, but they are powered with fluorocarbons, which add to environmental pollution, as Dr Balmes discusses elsewhere in the proceedings of this conference.[16] Additional contamination occurs from direct release of aerosol from test doses or upon misuse and discoordination by the patient. Because more than 50% of the aerosol particles may be >10 μm in size and therefore not respirable, various spacers have been used both to increase the effectiveness of aerosol delivery and to minimize environmental contamination. Finally, some aerosol from the MDI will be in the form of particles <1 μm in size and may be exhaled even after a breath-hold, but the mass of such contamination is extremely low. Overall, the environmental contamination from MDIs is minimal, and, because generally they are used privately by the patient, there is no direct danger to the health-care worker. Pentamidine may be deliverable by an MDI, but it is not currently available in this form.

Rotahalers, delivering powdered drug, are currently available for beta agonists. If more drugs such as steroids and cromolyn were made available in powdered form, this device might provide a solution to fluorocarbon contamination and provide a closed system for the medication. The particle size may be large, but the unused powder generally is trapped in the container.

Health-care workers are most frequently involved in the delivery of aerosols from nebulizers. Particularly in the hospital setting, aerosols are generally administered via open systems, all of which directly nebulize medication into the atmosphere, at least during patient exhalation. Face hoods or loose-fitting masks do little to control aerosol contamination of the environment, but aerosols delivered via mouthpiece, sealed face mask, T-piece, or ventilator are in a nominally closed system if an exhaust filter is used. In practice, exhaust filters are seldom used except when a recognized toxic agent such as ribavirin or pentamidine is nebulized.

Most systems nebulize continuously, so that during patient exhalation, fresh aerosol is fed directly into the exhaust pathway; if nebulizer flow is high enough, this also occurs during patient inhalation. This wastes medication and adds to environmental contamination. Demand-valve systems are possible, but the availability and use of such devices are very limited, even for potentially toxic aerosols such as pentamidine. A simple and effective alternative is the Y-piece, or thumb control, shown in Figure 1. The patient is instructed to occlude the opening when inhaling (which directs the pressurized gas into the nebulizer) and to uncover the opening when exhaling or not using the device (which allows the pressurized gas to leave the opening instead of entering the nebulizer). This is

particularly useful during pentamidine treatments because, when an unexpected cough occurs, the patient usually automatically releases the thumb control, and aerosol is not created to contaminate the room. Unfortunately, use of a thumb control is not usually recommended because this method prolongs the time for aerosolization of all the medication in the nebulizer and because some patients find it difficult to coordinate use of the thumb control with their breathing. Finally, when pentamidine is nebulized, interrupting aerosolization in this manner may clog the nebulizer due to the relative insolubility of the drug, particularly as the concentration increases and the temperature decreases; aerosol may then precipitate during the stagnant, no-flow period.

The potential for environmental contamination can be reduced if the dose of medication and the delivery time can be reduced. Smaldone and coworkers have suggested the use of another system, the AeroTech II, which may deliver 2.5-5 times more pentamidine to the lung, in a given period of time, than does the Respirgard system.[17] The AeroTech II can deliver 150 mg of pentamidine in 10-15 minutes, compared to the 15-60 minutes the Respirgard II takes to deliver 300 mg.[18] However, in that study, 15 of 23 patients coughed with the AeroTech II, whereas only 8 coughed with the Respirgard. Both devices were used without thumb controls or automatic shutoffs, and therefore the potential for environmental contamination was probably greater with the system that provoked more frequent coughs, increasing the time when aerosol was flowing out the exhaust pathway and not to the patient.

Other delivery systems, including ultrasonic nebulizers, have been proposed as more efficient, but published data are largely in abstracts,[19-21] and further evaluation is necessary. The characteristics of various brands of jet and ultrasonic nebulizers have been summarized by Corkery et al;[6] this information is shown in Table 2. It should be noted

Table 2. Features of Jet and Ultrasonic Nebulizers Used To Deliver Pentamidine*

Device	MMAD† (μm)	GSD	Reservoir for Aerosol during Exhalation?	Expiratory Filter?	Comments
Jet Nebulizers					
AeroTech II	2.0	+2.5‡	No	Optional	10-15 L/min flow
Centimist	1.1	+2.2§	Yes	No	9 L/min flow
FanJET	4.3	+2.5‡	No	Optional	7 L/min flow
Respirgard II	0.93	+1.8‡	Yes	Yes	7 L/min flow
System 22	1.3‖	N.A.	No	No	7 L/min flow
UltraVent	0.25	+2.0¶	No	Yes	11-14 L/min flow
Ultrasonic Nebulizers					
FISONeb	5.0	+2.0‡	Yes	No	Intermittent use trigger
Green Machine	> 12.0	N.A.	Yes	No	Intermittent use trigger
Portasonic	1.6	+2.2‡	Yes	Optional	Continuous flow
Pulmosonic	4.2	+2.3‡	Yes	No	Continuous flow

* Adapted, with permission, from Reference 6.

† MMAD = mean mass aerodynamic diameter; GSD = geometric standard deviation; N.A. = not available (not noted or not measured).

‡ Particle size measured as in Reference 8.

§ Particle size measured under condition of simulated breathing, as in Reference 20.

‖ Particle size measured by Malvern 2400 laser diffraction particle size, as in Godfrey-Faussett P, Miller RF, Semple SJ. Nebulised pentamidine (letter). Lancet 1988;1:645-646.

¶ Particle size measured by cascade impactor, as in Sirr SA, Juenemann DJ, Tom H, Boudrea RJ, Chandler RP, Loken MK. Effect of ethanol on droplet size, efficiency of delivery, and clearance characteristics of technetium-99m DTPA aerosol. J Nucl Med 1985;26:643-646.

that several of the systems have no exhaust filters, and none has an automated shutoff mechanism.

Environmental contamination can be reduced, even with continuous nebulization, if adequate exhaust filtration is possible. Few data have been published on the effectiveness of these filters in clinical use, but the characteristics of the filter materials, as attested to by their providers, are listed in Table 3. We will now consider the effectiveness of these filters in clinical situations, as well as room ventilation and other methods of controlling environmental contamination.

Table 3. Aerosol and Particulate Filters

Type of Filter	Efficiency	Description & Comments
Ultra-high efficiency	100%	Ceramic, hydrophobic Pall #BB50t
	99.9%	Polypropylene 3M Filtrate
	99.9%	Nylon, polyester Pall #PF305
High efficiency	90-99%	Wet laid paper or fiberglass, hydrophilic
Medium efficiency	60-90%	Compressed glass or cellulose
Roughing filters	10-60%	Loose-pack fibers
Electrostatic	60-90%	Requires maintenance

Control of Environmental Contamination

Despite all the care taken in methods of delivery, environmental contamination occurs by exhalation, cough, and direct aerosolization into the atmosphere. Occupational exposure to pentamidine aerosol was reported by Montgomery et al in 1990.[22] They sampled air in a pentamidine aerosol clinic at San Francisco General Hospital where no ventilation system was operating except an open door to the 36-cubic-meter room. They found only $4.5 \pm 3.6 \times 10^{-5}$ mg/m^3 of pentamidine from three different air samples over a 4-hour period. This would result in only a 4.9-microgram (μg) annual exposure to a health-care worker exposed 8 hours/day for 225 days, breathing 6 L/min, with an assumed high retention of aerosol.[23]

Dr Gary S Ogawa, Director of the Pharmacy at the University of Southern California, found no measurable pentamidine in air sampled next to 3 patients receiving pentamidine aerosol over a 4-hour period in a small room with ventilation that provided approximately six air changes per hour (personal communication, December 1990). He also measured pentamidine levels on either side of the Marquest exhalation filter, and found 19, 24, and 10 mg on the upstream sides of the three patients' filters but immeasurable amounts on the downstream sides. However, this may be misleading, as will be discussed hereafter.

Despite these optimistically low values of environmental contamination by pentamidine, there remains the possibility of greater contamination in less than optimal daily working conditions. In order to simulate a worst-case situation, we aerosolized pentamidine in a closed body plethysmograph for 1, 5, 10, and 15 minutes while air samples were collected at 2 L/min through each of three filter pumps in the box. The results are shown in Table 4. There was an expected increase in concentration to quite high levels of 19.5 μg/L after 15 minutes of nebulization into this closed space; there was an accumulation of pentamidine in the box, as only the 7 L/min flow of gas used for nebulization was leaving the box, which totaled approximately 1,500 liters of gas. During the first minute, the concentration levels of pentamidine were below detection (< 4.8 μg), but they became detectable with longer nebulization. Calculation of 1-minute leaks led to pentamidine concentrations of 1.85-2.6 μg/L (Table 4, Column D). A health-care worker in the immediate vicinity of the leak would inhale 4-6 μg/min (Table 4, Column E), which is the yearly exposure calculated by Montgomery et al.[22] using the same assumptions as those authors (ie, $\dot{V}_E = 6$ L/min, and 40% retention in the lung). Though this experiment simulated the worst-case situtation, as there was virtually no ventilation or chance for dispersion of the aerosol, it nevertheless emphasizes the potential for significant exposure to a health-care worker standing next to an aerosol coming out of a nebulizer removed from the patient's mouth for only 1 minute during cough, rest, or conversation.

The air leaving the box was passed through two filters used in two commercially available devices for delivering pentamidine aerosol, Hospitek and Marquest. The amounts of pentamidine measured on each side of the filters and the total amount

Table 4. Study of Worst-Case Pentamidine Aerosol Contamination in Body Plethysmograph*

A Nebulizing Time (Min)	(Total)	B Total Pentamidine (μg) (avg of 3 filters) (V_I = 2 L/min)	C Avg Concentration of Pentamidine in Box (μg/L)	D Rate of Increase of Pentamidine in Box† (μg/min)	E Potential Inhaled Pentamidine with 1-min Leak‡ (μg/min)
0-1	1	< 4.8	< 2.4	—	—
0-6	5	45.6	4.6	1.85	4.4
6-16	10	249	12.5	2.5	6.0
16-31	15	585	19.5	2.6	6.2

* See text for details of experiment.
† Assumes linear accumulation of pentamidine in box during nebulization.
‡ Assumes the concentration in Column D, V_E 6 L/min, and 40% retention in the lung.

of pentamidine in each filter are shown in Table 5. First and most important is the fact that >30% of the pentamidine passed through the first filter (Hospitek), indicating the inadequacy of that particular filter. The second point to emphasize is that merely eluting pentamidine off the surface of the downstream side does not ensure the efficiency of the filter; as the aerosol passes through the filter, it does not deposit on the downstream side. It is necessary to place a second filter and measure the total amount of material in that second filter by washing the dissolving solution (in this case, water) through the filter because only a portion of material will be captured by simply washing the surface. Therefore, Dr Ogawa's data referred to earlier may be misleading because only the surface of the downstream side was tested; pentamidine could have passed into the room air, but the six exchanges of ventilation per hour may have been sufficient to keep the concentration below detectable levels.

Table 5. Pentamidine Concentration from Filters Used in Two Devices in Body Plethysmograph*

Site	First Filter (Hospitek) in μg	Second Filter (Marquest) in μg
Upstream side	1,102	< 63
Downstream side	65	< 63
Flush through	210	612
Total and %	1,377 (69%)	612 (31%)

*See text for details of experiment.

Clearly, additional data of this sort must be collected to test the adequacy of the filters in a system.

Perhaps of greater concern is the environmental contamination by the patient population's cough aerosols. In particular, tuberculosis has been recognized as an increasingly common infection in the AIDS population.[24] For control of cough aerosols,[24] one must turn to room ventilation, filtration of air, and potential sterilization of air with ultraviolet radiation.

Room Ventilation

Downdraft ventilation and positive-pressure rooms have been used to minimize infection in highly susceptible patients, such as those having bone-marrow transplant or orthopedic joint-replacement surgery. The opposite occurs when aerosol and cough containment is the problem; here, negative-pressure rooms are desirable to prevent spread of contaminants to other areas. However, the effectiveness of room ventilation to control environmental contamination is questionable.

In the early 1900s, it was recommended that fresh-air ventilation be a generous 30 cubic feet/min/person to control body odor, not infection. This was reduced to 10 cubic feet/person in 1930; in 1973, with the rise in the price of heating oil, even lower standards were introduced.[23] Ventilation standards for health-care facilities have been published by the Federal Health Resources and Services Administration[25] and the American Society of Heating, Refrigerating, and Air Conditioning Engineers;[26] the current recommendation is 20 cubic feet/min/

person.[26] The usually cited six changes of room air/hour is based on a > 99% removal of particulates, assuming adequacy of filtration or introduction of clean outdoor air. Problems with filters and buildup of toxic vapors or very small particulates (< 0.1 μm) would reduce the effectiveness of recirculated ventilation. Even if ventilation is adequate, the following example will emphasize further the inadequacy of ventilation to protect the health-care worker. If a pentamidine-aerosol treatment room's dimensions were $10 \times 20 \times 10$ feet (a volume of 2,000 cubic feet) and it contained five patients, then 10 cubic feet/min/person would mean $5 \times 10 \times 60 = 3{,}000$ cubic feet/hour, or only 1.5 changes/hour; this would result in removal of < 90% of particulates. To achieve six changes/hour would require 40 cubic feet/min/person, twice the current recommendation, a somewhat costly but still achievable level of ventilation. However, it was shown many years ago (1967) by Riley,[27] and more recently re-emphasized by Riley and Nardell,[28] that in a situation where an infectious patient is actively coughing into the air, resulting in 1 to 12 "quanta of infectious doses," even 125 cubic feet/min/person is inadequate. Such ventilation is unrealistic and too costly and still not protective against tuberculosis. The situation may even be 20 times worse in a bronchoscopy situation, where as many as 250 "quanta" may be released into the air.[29]

Ultraviolet Light

Ultraviolet light was initially shown, by Wells et al in 1942, to be effective in controlling measles contagion.[30] Subsequent work by Riley et al,[31] in 1962, demonstrated the susceptibility of a number of infectious aerosols to ultraviolet light. They further estimated that efficient use of ultraviolet radiation may be equivalent to room ventilation as high as 100 cubic feet/min/person. As pointed out here earlier, even that is inadequate when a highly infectious subject is coughing, particularly in the direct vicinity of a health-care worker. Furthermore, the effectiveness of ultraviolet light may be much less, particularly in hospital rooms where ventilation is directed downward from the ceiling. The ultraviolet fixture, which is generally placed 1-2 feet from the ceiling, is therefore less effective. Dr Janet Mocher of the California State Department of Public Health and the National Institute of Occupational Safety and Health (NIOSH) are currently re-evaluating the effectiveness and safety of ultraviolet light. There is concern that ultraviolet radiation may add yet further risks to health-care workers. Improper use of ultraviolet light, or excess exposure, may produce photo damage to the eye, skin, and, most seriously, the immune system, with a potential for increased carcinogenesis.[32]

The potential bypass of exhaust filters, the absence of effective room ventilation, and the questionable efficacy of ultraviolet radiation have led to the recommendation of the use of special containment areas for potentially toxic aerosols and highly infectious patients. A double-hood system has been described by Charney et al for the control of ribavirin aerosol given to infants.[2] For delivery of pentamidine or perhaps for sputum induction, an enclosed booth (Emerson Corp), plastic hoods (Peace Medical), or exhaust cubicles that may be either mobile or fixed—as developed by Dr Charney at San Francisco General Hospital—have been proposed. By the use of high-flow pumps and high-efficiency filtration, these devices directly contain or exhaust both the aerosol and the patient's cough effluent; however, they do separate the patient from the health-care worker, and they would not be feasible for severely ill hospitalized patients or during specialized procedures such as bronchoscopy or nasotracheal lavage. For these situations, direct protection of the health-care worker is the only choice.

Direct Protection of the Health-Care Worker

Since the middle of the 19th century, when Lister and Semmelweis described the germ theory of disease—hand-washing, gloves, and surgical masks have been used religiously. Disinfectant soap is only temporarily and partially effective; gloves are frequently pierced by needles; and masks are only now being carefully evaluated and shown to be only partially effective as protection for the patient and of minimal benefit to the health-care worker. It was as late as 1980 that the leakage of bacteria around the sides of masks was emphasized as a source of infection of the patient.[33] It is necessary to wear a hood that contains the leaks around the sides and chin portion of the mask to more fully contain the bacteria. Similarly, though a surgical mask may prevent the inhalation of aerosols through the mask, even large-diameter particles with the largest mass of offending agents will readily pass around the edges of loose-fitting masks.

The most attention to mask-effectiveness has been paid primarily in the industrial setting. Studies by Tuomi published in 1985 showed that the filtration mass efficiency of 4 loose-fitting face masks varied from 33-81%.[34] In general, the filter materials were good, with >95% efficiency for particles >5 μm, but there was great variation for smaller particles. One mask was <10% effective for particles <2 μm, while the best of the four masks was only 50-70% effective for these smaller particles. In another study, by Chen et al,[35] published in 1990, Tuomi's findings were confirmed and extended to show a 5-20% leakage of small particles through masks when flowrates were increased from 5 L/min to 32 and 95 L/min, as might occur with heavy exertion. Other studies have demonstrated the almost zero efficiency of cheap disposable paper masks, versus the 78-100% efficiency of synthetic or glass fiber materials[36] (Table 6).

Table 6. Characteristics and Costs of a Mask and Protective Respirators

Type	Material	Efficiency*	Fit Test†	Cost
Surgical	Paper	0-80%	—	$0.12-$0.50
3M #8710	Polypropylene	99%	300:1	$0.70
3M #9970	Polypropylene	99.99%	2,000:1	$5.50

* From References 33 to 35.

† Ratio of particulate or aerosol in ambient air compared to that passing through the filter.

To protect the health-care worker from the small-particle aerosols produced by pentamidine and ribavirin, a high-quality synthetic-fiber mask with good fit is needed. Masks are now available that achieve or even exceed the efficiency of replaceable, cartridge face masks (Table 6). These masks also need to have an effective seal that meets NIOSH/MSHA standards. Mask-fit testing and safety programs need to be instituted if high-efficiency masks are to be worn by health-care workers. However, the use of such masks over prolonged periods of patient care has not been studied, is not practical, and is not the preferred or recommended method for effective protection of the health-care worker except during specialized procedures such as bronchoscopy, sputum induction, or treatment of patients known to be infectious.

Conclusions and Recommendations

Containment of potentially toxic aerosols remains an inadequately studied subject. The actual degree and risk of exposure to pentamidine have not been determined. In the future, parallel protocols to determine levels of exposure and risks to health-care workers need to be instituted simultaneously during clinical trials of potentially toxic aerosolized agents. Control of exhaust aerosols is feasible with proper methods of aerosol administration and exhaust filtration. Development of automatic shutoff devices for nebulizers and testing to determine the adequacy of filters need to be emphasized. Control of infectious diseases resulting from cough aerosols is of equal—and in many situations, higher—priority. Most importance must be placed on case control and recognition of patients with infectious diseases because room ventilation and ultraviolet light are not always adequate measures, isolation of all patients in enclosures is not possible, and effective long-term use of protective masks or respirators by health-care workers is not practical. Nevertheless, negative-pressure rooms with at least six air changes per hour, careful and proper use of ultraviolet radiation, and protective masks should all be available in pentamidine-aerosol, bronchoscopy, and sputum-induction clinics. An alternate strategy, and perhaps more economic and effective, may be the use of containment areas, booths, or exhaust hoods—particularly when adequate ventilation is not available and the patient population is at high risk for tuberculosis and other unrecognized or inadequately treated infectious diseases. Guidelines for preventing tuberculosis transmission, including more specific recommendations for specific hospital and health-facility situations, are available from the Centers for Disease Control.[37]

ACKNOWLEDGMENTS

We are grateful to Sue Marino for her administrative and clerical support of this project.

REFERENCES

1. Kern DG, Frumkin H. Asthma in respiratory therapists. Ann Intern Med 1989;110:767-773.
2. Charney W, Corkery KJ, Kraemer R, Wugofski L. Engineering and administrative controls to contain aerosolized ribavirin: results of simulation and application to one patient. Respir Care 1990;35:1042-1047.
3. Waskin H. Toxicology of antimicrobial aerosols: a review of aerosolized ribavirin and pentamidine. Respir Care 1991;36:1026-1036.

4. Fallat RJ, Kandal K, Feigal D. Pentamidine aerosol (PA) to prevent pneumocystis pneumonia (PCP) (abstract). Am Rev Respir Dis 1988;137(4, Part 2):120.
5. Leoung GS, Feigal DW Jr, Montgomery AB, Corkery K, Wardlaw L, Adams M, et al. Aerosolized pentamidine for prophylaxis against *Pneumocystis carinii* pneumonia: the San Francisco community prophylaxis trial. N Engl J Med 1990;323:769-775.
6. Corkery KJ, Luce JM, Montgomery AB. Aerosolized pentamidine for treatment and prophylaxis of *Pneumocystis carinii* pneumonia: an update. Respir Care 1988;33:676-685.
7. Montgomery AB, Debs RJ, Luce JM, Corkery KJ, Turner J, Brunette EN, et al. Aerosolised pentamidine as sole therapy for *Pneumocystis carinii* pneumonia in patients with acquired immunodeficiency syndrome. Lancet 1987;2:480-483.
8. Montgomery AB, Debs RJ, Luce JM, Corkery KJ, Turner J, Brunette EN, et al. Selective delivery of pentamidine to the lung by aerosol. Am Rev Respir Dis 1988;137:477-478.
9. Nebupent monograph. Rosemont IL: Lyphomed Inc, 1989.
10. Corkery KJ, Montgomery AB, Montanti R, Fine JM. Airway effects of aerosolized pentamidine isethionate (abstract). Am Rev Respir Dis 1990;141(4, Part 2):A152.
11. Debs R, Brunette E, Fuchs H, Lin E, Shah M, Hargis A, et al. Biodistribution, tissue reaction, and lung retention of pentamidine aerosolized as three different salts. Am Rev Respir Dis 1990;142:1164-1167.
12. Lowery S, Fallat RJ, Montgomery AB, Berge J. Changing patterns of *Pneumocystis carinii* pneumonia on pentamidine aerosol prophylaxis. Abstract from IV International Conference on AIDS, Stockholm, 1988.
13. Wardlaw LA, Montgomery AB, Corkery KJ, Abrams DI, Feigal DW, Leoung GS. Pneumothorax in patients receiving aerosol pentamidine prophylaxis for *Pneumocystis carinii* pneumonia (abstract). Am Rev Respir Dis 1990;141(4, Part 2):A152.
14. Gude JK. Selective delivery of pentamidine to the lung by aerosol (letter). Am Rev Respir Dis 1989;139:1060.
15. Ghedira H, Regnard J, Dessanges JF, Lockhart A, Marsac J, Lacronique J. Chronic cough and bronchial hyperresponsiveness in AIDS patients treated with aerosolized pentamidine (abstract). Am Rev Respir Dis 1990;141(4, Part 2):A151.
16. Balmes JR. Propellant gases in metered dose inhalers: their impact on the global environment. Respir Care 1991;36:1037-1044.
17. Smaldone GC, Fuhrer J, Steigbigel RT. Quantitative deposition of aerosolized pentamidine in AIDS (abstract). Am Rev Respir Dis 1990;141(4, Part 2):A150.
18. Vinciguerra C, Smaldone G. Treatment time and patient tolerance for pentamidine delivery by Respirgard II and AeroTech II. Respir Care 1990;35:1037-1041.
19. Dautzenberg B, Meignan M, Bouchikhi A, Antoun F, braga M Roy F, Becquemin MH, et al. Comparison of 5 devices for pentamidine aerosol administration (abstract). Am Rev Respir Dis 1990;141(4, Part 2):A153.
20. Howite JS, Gorvoy JD, Smaldone GC. Quantitative deposition of aerosolized gentamicin in cystic fibrosis. Am Rev Respir Dis 1987;136:1445-1449.
21. Howite JS, Baskin MI, Sheetz MS, Abd AG. Comparison of delivered dose and regional distribution of aerosolized pentamidine using different delivery systems (abstract). Am Rev Respir Dis 1990;141(4, Part 2):A153.
22. Montgomery AB, Corkery KJ, Brunette ER, Leoung GS, Waskin H, Debs RJ. Occupational exposure to aerosolized pentamidine. Chest 1990;98:386-388.
23. Nardell EA, Keegan J, Cheney SA, Etkind SC. Airborne infection: the theoretical limits of protection achievable by building ventilation. Am Rev Respir Dis (in press) 1991.
24. Centers for Disease Control. Tuberculosis and acquired immunodeficiency syndrome, New York City. MMWR 1987;36:785-795.
25. Guidelines for construction and equipment of hospital and medical facilities, 1984. Rockville MD: U.S. Dept of Health and Human Services, Health Resources and Services Administration, Publication No. (HRSA) 84-14500.
26. The American Society of Heating, Refrigerating, and Air Conditioning Engineers (ASHRAE). Ventilation for acceptable indoor air quality. Standard 62. Atlanta: ASHRAE, 1989.
27. Riley RL. The hazard is relative. Am Rev Respir Dis 1967;96:623-635.
28. Riley RL, Nardell EA. Clearing the air: the theory and application of ultraviolet air disinfection. Am Rev Respir Dis 1989;139:1286-1294.
29. Cantazaro A. Nosocomial tuberculosis. Am Rev Respir Dis 1982;125:559-562.
30. Wells WF, Wells MW, Wilder TS. The environmental control of epidemic contagion. I. An epidemiologic study of radiant disinfection of air in day schools. Am J Hygiene 1942;35:97-121.
31. Riley RL, Mills CC, O'Grady F, Sultan LU, Wittestadt F, Shivpuri DN. Infectiousness of air from a tuberculosis ward: ultraviolet irradiation of infected air; comparative infectiousness of different patients. Am Rev Respir Dis 1962;85:511-525.
32. Council on Scientific Affairs, American Medical Association (AMA). Harmful effects of ultraviolet radiation. Chicago: AMA, 1984.
33. Ha'eri GB, Wiley AM. The efficacy of standard surgical face masks: an investigation using "tracer particles." Clin Orthop 1980;148:160-162.
34. Tuomi T. Face seal leakage of half masks and surgical masks. Am Ind Hyg Assoc J 1985;46:308-312.
35. Chen CC, Ruuskanen J, Pilacinski W, Willeke K. Filter and leak penetration characteristics of a dust and mist filtering facepiece. Am Ind Hyg Assoc J 1990;51:632-639.
36. Rogers KB. An investigation into the efficacy of disposable face masks. J Clin Pathol 1980;33:1086-1091.
37. Centers for Disease Control. Guidelines for preventing the transmission of tuberculosis in health-care settings, with special focus on HIV-related issues. MMWR 1990;39 (RR-17):1-29.

Control of Tuberculosis during Aerosol Therapy Administration

Richard E Chaisson MD and Sharon McAvinue RN

Introduction

Aerosol therapy has gained an important position in the treatment of selected groups of patients in recent years. In particular, aerosolized pentamidine therapy has become an increasingly popular method to prevent *Pneumocystis carinii* pneumonia in patients immunocompromised by human immunodeficiency virus (HIV) infection or other conditions.[1-3] While the selective delivery of pentamidine to the alveoli by aerosol administration has been effective in avoiding systemic toxicity and in preventing *P carinii* pneumonia, problems with this treatment regimen have occurred. Several recent reports have implicated pentamidine aerosol therapy with the transmission of *Mycobacterium tuberculosis* to other immunocompromised patients and to health-care workers at HIV care centers.[4,5]

The association of pentamidine aerosol therapy with tuberculosis transmission is not surprising. Aerosolized pentamidine is a potent inducer of bronchospasm and cough, and reactivation of *M tuberculosis* infection is a common complication of advanced HIV infection.[6] In the first report of pentamidine aerosol therapy for treatment of acute *P carinii* pneumonia, Montgomery et al found that 14 of 15 patients experienced exacerbation of cough with treatment.[7] In subsequent studies of preventive pentamidine aerosol therapy, cough and bronchospasm have been reported frequently, though less often than in patients being treated for active *P carinii* pneumonia. Leoung and co-workers found that 31-40% of patients with advanced HIV disease who received various doses of pentamidine aerosol via the Respirgard II nebulizer (Marquest Medical Products, Englewood CO) experienced severe cough (Table 1).[2] Delivery of pentamidine aerosol with the FISONeb nebulizer (Fisons Corp, Rochester NY) in another study resulted in cough in 65% of patients during their first treatment and 53% of patients after 16 treatments, significantly higher proportions than in saline-treated controls (Table 2).[8] Thus, pentamidine aerosol therapy will frequently elicit cough, and high-volume-delivery devices may produce cough more often.

Table 1. Pentamidine Aerosol Therapy and Cough in a Study Using a Respirgard II Nebulizer*

Pentamidine Dose	No. Severe Cough/ No. Patients	% Severe Cough
30 mg	42/135	31%
150 mg	54/134	40%
300 mg	53/139	38%

*Adapted with permission, from Reference 2.

Patients with HIV infection are at increased risk for a number of respiratory infections, some of which are potentially transmissible by coughing (Table 3). While transmission of respiratory viruses during aerosol therapy is of some concern, transmission of *M tuberculosis* is a major clinical and

Dr Chaisson is Director, AIDS Service, and Assistant Professor of Medicine, Epidemiology and International Health; and Ms McAvinue is Clinical Research Nurse—Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

A version of this paper was presented by Dr Chaisson during the Consensus Conference on Aerosol Delivery, sponsored by the American Association for Respiratory Care, the American Respiratory Care Foundation, and the journal RESPIRATORY CARE, January 10-12, 1991, in Cancun, Mexico.

Table 2. Frequency of Cough in Patients Receiving Placebo or Pentamidine in a FISONeb Nebulizer*

	Treatment Group	
Phase of Treatment	Placebo	Pentamidine 60 mg†
1st treatment	4/19 (21%)	11/17 (65%)
10th treatment	3/19 (16%)	10/16 (63%)
16th treatment	0/13 (0%)	8/15 (53%)

*Adapted, with permission, from Reference 8.
†$p < 0.05$.

public health issue. Impairment of cell-mediated immunity by HIV infection results in increased risk of reactivation of tuberculosis[9] and increased susceptibility to progressive primary tuberculosis.[10] In the first 50 weeks of 1990, the tuberculosis case rate in the United States increased 8% over the 1989 rate.[11] It is estimated that since 1985 there have been approximately 25,000 excess cases of tuberculosis in the United States, largely a consequence of the HIV epidemic. Studies matching AIDS and Tuberculosis Registries in a number of jurisdictions have shown that between 2 and 9% of AIDS cases also have tuberculosis (Table 4).[12] The prevalence of tuberculosis in patients with AIDS or HIV infection is higher in immigrants from developing countries, Blacks, Hispanics, intravenous drug users, and prisoners than in other groups.[6,9,13-15] For example, approximately 70% of adults in some parts of Haiti have positive tuberculin skin tests,[16] and 22% of intravenous drug users in New York City are tuberculin positive,[9] indicating past infection with *M tuberculosis*. When HIV-induced immunosuppression occurs in these groups, high rates of tuberculosis can be expected. Tuberculosis has been reported in all categories of patients with HIV infection, however, and is a possible complication of pentamidine aerosol therapy in most settings. Consequently, strategies to prevent the transmission of airborne pathogens, particularly *M tuberculosis*, are needed for clinics and health-care facilities that provide pentamidine aerosol therapy.

Table 3. Potential Transmission Routes of Respiratory Infections in HIV Patients Receiving Aerosol Therapy

Airborne	Direct Contact	Other Routes
M tuberculosis	Adenovirus	*P carinii*
Influenza	Parainfluenza	*S pneumoniae*
Varicella zoster	Rhinovirus	*C neoformans*
Measles	RSV*	*H capsulatum*
Legionella	*H influenzae*	CMV
	Mycoplasma	

*RSV = respiratory syncytial virus. CMV = cytomegalo-virus.

Table 4. Association of AIDS and Tuberculosis in Registry Matching Studies*

Location/Time	% AIDS Cases with TB
San Francisco, 1981-1988	2%
Florida, 1981-1985	9%
New York City, 1981-1985	5%
Connecticut, 1982-1986	5%

*Reprinted, with permission, from Reference 12.

Transmission of *M Tuberculosis* and Aerosol Therapy

In 1989, the Centers for Disease Control (CDC) reported an outbreak of tuberculin skin-test conversions in health-care workers in a Florida HIV clinic.[4] The clinic provided primary care to AIDS patients, including 39 patients with pulmonary tuberculosis, 14 of whom were sputum smear-positive. In addition to the provision of pentamidine aerosol treatments to patients (including patients with tuberculosis), diagnostic sputum inductions were performed on individuals with smear-positive pulmonary tuberculosis. A case-control study of tuberculin convertors and controls indicated that being a full-time worker, working in the clinical care area of the building, being non-white, and being present during pentamidine aerosol therapy were all significantly more likely among convertors than controls. Interestingly, having face-to-face contact with an employee with sputum smear-negative tuberculosis was not associated with skin-test conversion. No data were given on exposure to patients undergoing sputum

induction. An investigation of building ventilation revealed that over 90% of air was recirculated in the building and that the pentamidine treatment and sputum-induction areas had positive air pressure relative to other clinic areas. A more recent and ominous report of transmission of multi-drug-resistant *M tuberculosis* to HIV-infected patients and to health-care workers at a Florida hospital also may be associated with aerosol therapy, though numerous other factors are clearly involved.[5] The common themes in both outbreaks are inadequate isolation of patients with suspected or known tuberculosis, administration of cough-inducing therapy to patients with active pulmonary infections, inadequate infection-control procedures during sputum induction, and substandard ventilation systems in health-care facilities with a large number of tuberculosis patients.

A number of factors determine the likelihood that a person with tuberculosis will transmit infection to susceptible contacts. *M tuberculosis* is transmitted person-to-person by droplet nuclei, 2- to 5-μm particles expelled during coughing, talking, singing, or sneezing, that contain one or more bacilli and that are distributed by random diffusion.[17] Factors involved in transmission from the source tuberculosis case include the number of bacilli in the lungs or other respiratory sites, the frequency of coughing, whether the mouth is covered during coughing, and whether antituberculosis chemotherapy is administered.[18] In a study of tuberculosis cases and household contacts younger than 14 years old, Loudon and Spohn found that tuberculin reactivity in contacts was strongly associated with the presence of acid-fast bacilli on sputum smears, radiographically advanced disease, and higher overnight total cough-counts in cases (Table 5).[19] Other studies have shown that close and frequent contact with tuberculosis cases is more likely to result in infection with *M tuberculosis* than casual, non-household contact.[20] Exposure to patients after the initiation of antituberculosis therapy is significantly less likely to result in infection in both guinea pigs and humans.[21,22] In the health-care setting, smear positivity, radiographically advanced disease, and exposure to untreated cases also predict infectivity.[23] Studies in the early chemotherapy era suggested that drug-resistant *M tuberculosis* may be less transmissible than drug-susceptible isolates. More recent studies (including multi-drug-resistant isolates of *M tuberculosis)* indicate that drug-resistant organisms can be easily transmitted to susceptible individuals.[5,21]

Table 5. Infectiousness of Tuberculosis Cases for Household Contacts Younger than 14 Years of Age*

Case Variable	Contacts % Tuberculin Reactors
Radiographic extent of disease	
Minimal	16.1
Moderately advanced	28.3
Far advanced	61.5
Bacteriologic status	
Culture negative	14.3
Culture positive/smear negative	21.4
Smear positive	44.3
Mean 8-hour overnight cough-count	
< 12	27.5
12-48	31.8
> 48	43.9

*Reprinted, with permission, from Reference 19.

Transmission of *M tuberculosis* by individuals with HIV infection and active tuberculosis appears no more likely than in non-HIV-infected tuberculosis patients (unpublished data, NYC Dept Health, Centers for Disease Control). In fact, some evidence suggests that HIV-related tuberculosis cases may be less infectious than non-HIV-related cases. Studies in Africa[24] and the United States[25] demonstrate that the frequency of positive sputum smears is significantly lower in HIV-seropositive persons with tuberculosis than in HIV-seronegative patients. In addition, several studies demonstrate that patients with HIV and tuberculosis have less radiographically advanced disease and fewer cavities, suggesting a decreased likelihood of transmitting infection.[13] Nevertheless, between 40 and 60% of HIV-related tuberculosis cases have

positive sputum smears, and the potential for transmission is very real.[12,26] Thus, HIV-infected patients at high risk for tuberculosis who undergo cough-producing procedures pose the potential risk of transmitting *M tuberculosis* in the health-care setting.

Preventing Transmission of Infections during Aerosol Therapy

Several approaches to the control of infections in health-care workers and others exposed to persons receiving pentamidine aerosol therapy are necessary (Table 6). First and foremost is the prevention of infections or disease, particularly tuberculosis, in patients with advanced HIV infection.[27] Second, early diagnosis and treatment of potentially infectious processes, and isolation of patients suspected to have tuberculosis, are essential. Third, reducing the likelihood of generating cough during aerosol therapy may also be important in reducing tuberculosis transmission. Fourth, a number of engineering controls can be employed that will substantially reduce the probability of transmission of *M tuberculosis* or other respiratory pathogens when an infected individual is treated with pentamidine aerosol. Finally, personal protection devices can be used to prevent acquisition of *M tuberculosis* by health-care workers when other measures are not feasible or adequate.[28]

Table 6. Approaches To Preventing TB Transmission during Aerosol Therapy

TB chemoprophylaxis for all at-risk patients
Rapid diagnosis and management of TB
Reduce cough with aerosol therapy
Ventilation controls
Air filters
Disinfection with UV light
Protective devices

Prevention of tuberculosis in persons with HIV infection is perhaps the most important strategy for controlling nosocomial transmission of *M tuberculosis*. The risk of progressing from inactive infection (usually indicated by a positive purified protein derivative [PPD] skin test) to active disease is extremely high in persons with HIV infection. Three prospective cohort studies have demonstrated that the risk of developing tuberculosis for HIV-infected persons with a positive tuberculin skin test or in a group at very high risk for *M tuberculosis* infection is higher than in any patient population ever studied (Table 7).[9,29,30] The CDC has recommended that all HIV-seropositive persons with a positive PPD, defined as greater than 5-mm induration, receive chemoprophylaxis with isoniazid for 12 months.[31,32] Isoniazid prophylaxis has been shown to significantly reduce the risk of developing active tuberculosis in HIV-infected adults studied in Zambia.[33] A number of studies are currently under way evaluating the safety and efficacy of shorter courses of rifampin, with or without pyrazinamide, in preventing tuberculosis in HIV-infected persons.[34]

Identification of persons with HIV infection at risk for tuberculosis may be difficult, as cutaneous anergy is an early finding in HIV infection.[35] Studies of patients with HIV infection and active tuberculosis show that 39-65% have a greater than 10-mm response to PPD.[12] As noted, however, the CDC now advises that a 5-mm induration be used as the cutoff point for determining *M tuberculosis* infection in high-risk groups, including persons with HIV infection.[32] Studies in Haiti indicate that approximately 70% of asymptomatic, HIV-infected adults have a response ≥ 5 mm to PPD, similar to the proportion of HIV-seronegative adults with a ≥

Table 7. Risk of Tuberculosis in HIV-Infected Adults

Population/ Reference	Follow-Up Time	HIV-Positive No. with TB/Total (%)	HIV-Negative No. with TB/Total (%)
I.V. Drug Users, Bronx[9]	24 month	7/49 (14.0%)	0/62 (0%)
Postpartum Women, Zaire[29]	32 month	19/249 (7.6%)	1/310 (0.3%)
Adult Women, Rwanda[30]	24 month	20/473 (4.2%)	1/997 (0.1%)

10-mm response.[16] While the tuberculin skin test will not identify all HIV-infected persons who may benefit from chemoprophylaxis, it remains the best diagnostic tool available. All persons with newly diagnosed HIV infection should have a tuberculin skin test performed, and any patient with a ≥ 5-mm reaction, or a history of a positive reaction, should receive isoniazid prophylaxis. In some populations of HIV-infected patients at increased risk of *M tuberculosis* infection, however, clinicians may wish to administer chemoprophylaxis irrespective of tuberculin skin-test results.

Prompt diagnosis and treatment of tuberculosis is the next most important strategy for preventing transmission of *M tuberculosis* to household contacts and in health-care settings. Undiagnosed tuberculosis remains the most common source of *M tuberculosis* infection in health-care workers. The two Florida outbreaks cited above involved tuberculosis cases that went undiagnosed for some time.[4,5] Patients with undiagnosed pulmonary disease should not receive pentamidine aerosol therapy. Rather, they should be referred for immediate clinical evaluation, including chest radiographs and, if appropriate, sputum induction or bronchoscopy.[36] Respiratory tract specimens from patients with HIV infection and pulmonary disease should always be sent for acid-fast stains and mycobacterial cultures. HIV-infected patients with undiagnosed pulmonary disease should be considered to be an infectious risk and should be subject to appropriate infection-control precautions, including use of masks and isolation rooms. If tuberculosis is diagnosed, infection-control precautions should be maintained until sputum smears are negative and the patient has received 2 weeks of antituberculosis therapy.[18] Pentamidine aerosol can be administered to patients with pulmonary tuberculosis who are receiving appropriate therapy and who have negative sputum smears.

Aerosol-therapy regimens should be designed to minimize the frequency of cough as an adverse reaction. Pentamidine isethionate can induce cough when delivered to the airways,[37] and other pentamidine salts may trigger bronchospasm equally often. Therefore, reducing airway delivery of pentamidine and maximizing alveolar delivery should enhance efficacy and reduce adverse reactions. Nebulizers that generate particles with a mass median aerodynamic diameter < 5 μm will maximize alveolar deposition and reduce airway delivery. The currently recommended nebulizer for administering pentamidine aerosol, the Respirgard II, generates particles in this size range. Nevertheless, even with appropriately sized particles, considerable airways deposition occurs, and other cough-reducing strategies may need to be employed. The rate at which pentamidine aerosol therapy is administered may affect the frequency of cough. Nebulizers that are highly efficient and deliver pentamidine rapidly may cause an increased frequency of cough and bronchospasm. In general, delivery systems that cause fewer adverse reactions are preferred. However, this concern needs to be balanced against other important issues such as cost, convenience, and time. Pretreatment of patients who experience cough during pentamidine aerosol therapy with inhaled beta agonists is highly effective.[2,7] Routine pretreatment should be reserved for those patients who have reacted to prior treatments with moderate-to-severe coughing. When cough develops during a treatment, pentamidine aerosol should be stopped and the patient treated with an inhaled beta agonist. A standard metered dose inhaler or other device designed for bronchodilator therapy should be used. When cough occurs, it is important that patients be instructed to cover their mouths. This seemingly obvious and simple maneuver will substantially reduce the number of infectious particles suspended in the air of a room.[38] Exhaust filters on hand-held nebulizers may also entrap coughed particles, but only if the patient keeps the mouthpiece in the mouth while coughing. Because patients are not likely to cough into a nebulizer, therapists administering aerosol therapy may wish to instruct patients to remove the mouthpiece and cover their mouths when they cough, for more effective control of infectious particles.

Environmental and engineering factors are extremely important, in addition to the patient and nebulizer factors listed above, in controlling infections in a health-care facility. Central to the control of infection (and drug exposure) is adequate ventilation. The number of air changes per hour, air pressure relative to adjacent areas, recirculation of air, and use of particle filters all contribute to con-

trol of infections in the health-care setting. Guidelines for ventilation of hospitals and other health facilities have been developed by the American Society of Heating, Refrigerating, and Air Conditioning Engineers (ASHRAE) (Table 8).[39] Guidelines for isolation rooms and infectious-disease laboratories call for a minimum of 6-10 air changes per hour and neutral or negative air pressure relative to adjacent areas. A single air change removes 63% of randomly distributed infectious particles within a room.[40] Six air changes will remove 99.2%, and 10 changes will remove 99.995% of infectious particles.[40] Increasing the number of air changes per hour decreases the amount of time a susceptible person within a room will be exposed to potentially infectious particles. Twenty air changes per hour will result in 99.2% clearance of infectious particles every 18 minutes. More frequent air changes will result in even faster and more efficient removal of infectious particles.

Table 8. Guidelines for Ventilation and Pressure within Hospital Areas*

Area	Pressure	Min. Air Changes per Hour	Exhaust	Recirculation
Operating room	+	15-25	Optional	No
Recovery room	+	6	Optional	No
Patient room	+/-	2	Optional	Optional
Isolation room	0	6	Yes	No
Treatment room	+/-	6	Optional	Optional
Infectious-disease lab	-	6	Yes	No

*Adapted, with permission, from Reference 39.

Positive air pressure will permit escape of infectious particles to adjacent patient care and waiting areas in most clinical settings, and should be avoided. While ASHRAE guidelines for inhalation-therapy settings and treatment rooms suggest positive and neutral pressure, respectively, the more stringent requirements for infectious-disease laboratories are more appropriate for aerosol therapy treatment rooms.[39] After removal from the treatment area, vented air should not be recirculated, but should be released outdoors. Exhaust ducts should be located away from areas used by people and at least 30 feet from air-intake ducts. Many facilities recirculate air in patient-care areas to reduce air-conditioning and heating costs. Therefore, special ventilation procedures for treatment rooms and isolation rooms are required. In addition to adequate ventilation, air filtering is necessary to reduce risk of transmission of infectious particles. Ventilation standards for hospitals recommend air-filtration systems that are 90% efficient in removing particulates.[39] For isolation rooms and infectious-disease laboratories, however, the use of high efficiency particle air (HEPA) filters is recommended. HEPA filters remove 99.97% of dioctylphthalate (DOP), a very small (0.3 μm) particle used to test filters. HEPA filters can be installed in exhaust air ducts, at exhaust outlets, or within treatment rooms. Use of HEPA filters is especially recommended when air recirculation is mandated by engineering or other constraints. HEPA filters should be properly installed to avoid system leaks, should be equipped with manometers to allow constant monitoring, and should be properly maintained.[28,39]

Several companies now market HEPA filtration systems designed for aerosol therapy or sputum induction. Figure 1 shows a benchtop HEPA filter hood that permits recirculation of filtered air within a room. The unit has a Plexiglas enclosure that patients face while receiving therapy that ensures entrainment of exhaust and exhaled air. A minimum air velocity of 30 m^3/min is maintained constantly. This type of unit can be incorporated into exhaust ductwork to vent outdoors instead of recirculating air within the room. A similar approach to a filtered hood is the use of a sealed booth for aerosol therapy. Commercially available booths are under negative pressure, have high-volume air exchange, and filter exhaust through HEPA filters prior to recirculating air within the room or venting it outdoors.

Disinfection of room air with ultraviolet (UV) light enjoys a special place in the history of public health as a method for reducing airborne infections.[40] Studies by Wells and colleagues in Pennsylvania schoolchildren in the 1930s demonstrated a marked reduction in measles in children whose classrooms were irradiated by UV light.[41] Riley and associates in the 1950s and 1960s

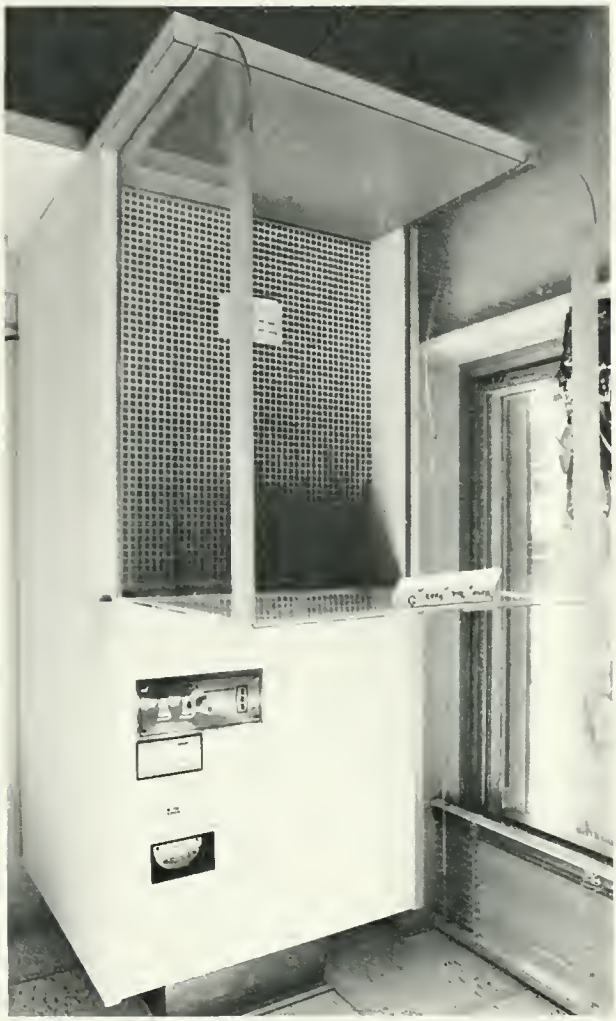


Fig. 1. Benchtop ventilation system for pentamidine aerosol therapy and sputum induction used at the Johns Hopkins Hospital HIV Clinic. Patients sit facing the hood. Air is drawn in at 30 cubic meters per minute and passes through a high efficiency particle air (HEPA) filter. Exhaust air enters an overhead duct and is vented outdoors. The equipment is from Laminar Flow Inc, Ivyland, Pennsylvania.

showed that guinea pigs breathing exhaust air from a tuberculosis ward could be completely protected from *M tuberculosis* infection when UV light was used.[21] UV-lighting systems have been used for years in tuberculosis wards, sputum-induction rooms, pulmonary function laboratories, and clinical laboratories. In addition, UV lights are sometimes used in ventilation ducts coming from these areas or from patient-care areas prior to recirculation. A number of considerations must be made for the use of UV light, however. Because UV light can cause skin and eye irritation and disease, human exposure must be avoided. Consequently, UV lights must be installed above eye level and baffled to prevent radiation of the lower zone of a room, and reflection off upper walls and ceilings must also be prevented.[40] Use of UV lighting in rooms with ceiling heights lower than 3 meters is, therefore, impractical. For sterilization to occur, air contaminated with infectious particles must be mixed and reach the upper zone of the room. The degree of sterilization also depends on the length of time that organisms are exposed to UV light. The effectiveness of UV-light sterilization is reduced by humidity above 60-70%.[38] While guidelines for health facilities generally require low air humidity, the generation of aerosols may raise the humidity in a treatment room to a level that would impede UV sterilization. Under optimal ventilation and filtering conditions there is little need for the addition of UV lighting. In fact, the high airflows that are likely to be most effective in removing infectious particles from a room may make UV light unnecessary and ineffective. Treatment areas with low air exchange rates and inadequate filtering may be equipped with UV lights as an alternative. However, UV light should not substitute for other recommended measures to prevent nosocomial transmission of infections. ASHRAE discourages the use of UV light as impractical and unproved. Further research on the role of UV light in reducing *M tuberculosis* transmission is needed.

A final approach to protecting health-care workers and others from acquiring infections from patients undergoing aerosol therapy is the use of personal protective devices. Properly fitting, high efficiency particulate respirators may complement other protective measures for individuals with intense exposure to patients with respiratory infections. Standard surgical face masks do not protect against respiratory infection because they often fit poorly and permit inhalation of particles through openings around the face.[42] Snugly fitting masks with high efficiency ratings may be protective and are commercially available. To be effective, such masks must be worn constantly while personnel are in the treatment area. Visitors and others entering the treatment area should also wear such masks.

The Occupational Safety and Health Administration rates particulate respirators and has approved several for preventing exposure to aerosolized chemicals and dusts. In general, these devices remove particles larger than 0.3 μm, and are appropriate for use in aerosol therapy treatment areas. The use of personal protective devices should not be substituted for appropriate clinical, environmental, and engineering controls.

Summary

In summary, despite the major benefits conferred by aerosol therapy, the risk of transmission of *M tuberculosis* remains a concern. The most effective approach to preventing nosocomial transmission of respiratory infections such as tuberculosis is to prevent disease in patients at risk, particularly those receiving aerosol therapy. Tuberculin skin tests should be applied to all HIV-infected persons and chemoprophylaxis administered to those with ≥ 5-mm reaction. Early detection and treatment of tuberculosis are essential to prevent transmission both inside and outside of health-care settings. Cough-reduction measures should be taken when giving pentamidine aerosol, and patients who do cough should cover their mouths. Proper ventilation of treatment areas with negative air pressure and at least 10 air changes per hour, and more if feasible, is essential. HEPA filters should be installed to cleanse exhaust air from treatment rooms, and air should not be recirculated. The use of UV light to disinfect air is recommended only for special situations. Finally, personal protective devices should be worn by health-care workers who are exposed to patients receiving aerosol therapy when other measures do not offer adequate protection.

REFERENCES

1. Girard P-M, Landman R, Gaudebout C, Lepretre A, Lottin P, Michon C, et al. Prevention of *Pneumocystis carinii* pneumonia relapse by pentamidine aerosol in zidovudine-treated AIDS patients. Lancet 1989;1:1348-1353.
2. Leoung GS, Feigal DW Jr, Montgomery AB, Corkery K, Wardlaw L, Adams M, et al. Aerosolized pentamidine for prophylaxis against *Pneumocystis carinii* pneumonia: the San Francisco community prophylaxis trial. N Engl J Med 1990;323:769-775.
3. Conte JE, Hollander H, Golden JA. Inhaled or reduced-dose intravenous pentamidine for *Pneumocystis carinii* pneumonia. Ann Intern Med 1987;107:495-498.
4. Centers for Disease Control. *Mycobacterium tuberculosis* transmission in a health clinic—Florida, 1988. MMWR 1989;38:256-264.
5. Centers for Disease Control. Nosocomial transmission of multidrug-resistant tuberculosis to health care workers and HIV-infected patients in an urban hospital—Florida. MMWR 1990;39:718-722.
6. Chaisson RE, Slutkin G. Tuberculosis and HIV infection. J Infect Dis 1989;159:96-100.
7. Montgomery AB, Debs RJ, Luce JM, Corkey KJ, Turner J, Burnette EN, et al. Aerosolised pentamidine as sole therapy for *Pneumocystis carinii* pneumonia in patients with acquired immunodeficiency syndrome. Lancet 1987;2:480-483.
8. Toronto Aerosolized Pentamidine Study (TAPS) Group. Acute pulmonary effects of aerosolized pentamidine: a randomized controlled study. Chest 1990;98:907-910.
9. Selwyn PA, Hartel D, Lewis VA, Schoenbaum EE, Vermund SH, Klein RS, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med 1989;320:545-550.
10. Di Perri G, Cruciani M, Danzi MC, Luzzati R, De-Checchi G, Malena M, et al. Nosocomial epidemic of active tuberculosis among HIV-infected patients. Lancet 1989;2:1502-1504.
11. Centers for Disease Control. Cases of specific notifiable diseases, United States, weeks ending December 1, 1990 and December 2, 1991 (48th week). MMWR 1990; 39:919.
12. Johnson MP, Chaisson RE. Tuberculosis and HIV disease. In: Jacobson MA, Volberding PA, eds. AIDS clinical review 1991. New York: Marcel Dekker, 1991:109-126.
13. Chaisson RE, Schecter GF, Theuer CP, Rutherford GW, Echenberg DF, Hopewell PC. Tuberculosis in patients with the acquired immunodeficiency syndrome: clinical features, response to therapy and outcome. Am Rev Respir Dis 1987;136:570-574.
14. Sunderam G, McDonald RJ, Maniatis T, Oleske J, Kapila R, Reichman LB. Tuberculosis as a manifestation of the acquired immunodeficiency syndrome (AIDS). JAMA 1986;256:362-366.
15. Braun MM, Truman BI, Maguire B, DiFerdinando GT Jr, Wormser G, Broaddus R, et al. Increasing incidence of tuberculosis in a prison inmate population: association with HIV infection. JAMA 1989;261:393-397.
16. Johnson M, Clermont HC, Coberly J, Chaisson R, Davies H, Eaton A, et al. Impact of HIV infection on response to tuberculin skin tests in Haitian adults (abstract). Am Rev Respir Dis 1991;143(4, Part 2):A280.
17. Wells WF. Aerodynamics of droplet nuclei. In: Wells WF, ed. Airborne contagion and air hygiene. Cambridge: Harvard University Press, 1955:13-19.

18. Hopewell PC. Factors influencing the transmission and infectivity of *Mycobacterium tuberculosis*: implications for clinical and public health practice. In: Sande MA, Hudson LD, Root RK, eds. Contemporary issues in infectious disease. Vol 5. New York: Churchill Livingstone, 1986:191-216.
19. Loudon RG, Spohn SK. Cough frequency and infectivity in patients with pulmonary tuberculosis. Am Rev Respir Dis 1969;99:109-112.
20. Grzybowski S, Barnett GD, Styblo K. Contacts of cases of active pulmonary tuberculosis. Bull Int Union Against Tuberc 1975;60:90.
21. Riley RL, Mills CC, O'Grady F, Sultan LU, Wittstadt F, Shivpuri DN. Infectiousness of air from a tuberculosis ward. Am Rev Respir Dis 1962;85:511-525.
22. Jindani A, Aber VR, Edwards EA, Mitchison DA. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. Am Rev Respir Dis 1980;121:939-949.
23. Kantor HS, Poblete R, Pusatrei SL. Nosocomial transmission of tuberculosis from unsuspected disease. Am J Med 1988;84:833-838.
24. Elliott AM, Luo N, Tembo G, Halwiindi B, Steerbergen G, Machiels L, et al. Impact of HIV on tuberculosis in Zambia: a cross-sectional study. Br Med J 1990;301: 412-415.
25. Klein NC, Duncanson FP, Lenox TH III, Pitta A, Cohen SC, Wormser GP. Use of mycobacterial smears in the diagnosis of pulmonary tuberculosis in AIDS/ARC patients. Chest 1989;95:1190-1192.
26. Small PM, Schecter GF, Goodman PC, Sande MA, Chaisson RE, Hopewell PC. Treatment of tuberculosis in patients with advanced human immunodeficiency virus infection. N Engl J Med 1991;324:289-294.
27. Chaisson RE. Prevention of opportunistic infections in patients with HIV infection. Maryland Med J 1990;39 (2):156-160.
28. Centers for Disease Control. Guidelines for preventing the transmission of tuberculosis in health-care settings, with special focus on HIV-related issues. MMWR 1990;39(RR-17):1-29.
29. Braun MM, Badi N, Ryder RW, Baende E, Mukadi Y, Nsuami M, et al. A retrospective cohort study of the risk of tuberculosis among women of childbearing age with HIV infection in Zaire. Am Rev Respir Dis 1991: 143:501-504.
30. Batungwanago J, Allen S, Bogaerts J, et al. Etude prospective du risque de tuberculose dans une cohorte de femmes HIV seropositives a Kigali, Rwanda (abstract WOD4). Kinshasa, Africa: Fifth International Conference on AIDS and Malignancies in Africa, Oct 10, 1990.
31. Centers for Disease Control. Diagnosis and management of mycobacterial infection and disease in persons with human T-lymphotropic virus type III/ lymphadenopathy-associated virus infection. MMWR 1986;35:448-452.
32. Centers for Disease Control. Tuberculosis and human immunodeficiency virus infection: recommendations of the Advisory Committee for the Elimination of Tuberculosis (ACET). MMWR 1989;38:236-238,243-250.
33. Wadhawan D, Hira S, Mwansa N, Tembo G, Perine PL. Isoniazid prophylaxis among patients with HIV-1 infection (abstract No. Th.B.510). San Francisco: Sixth International Conference on AIDS, June 21-24, 1990.
34. Lecoeur HF, Truffot-Pernot C, Grosset JH. Experimental short-course preventive therapy of tuberculosis with rifampin and pyrazinamide. Am Rev Respir Dis 1989;140:1189-1193.
35. MacDonell KB, Chmiel JS, Goldsmith J, Wallemark CB, Steinberg J, Byrers E, et al. Prognostic usefulness of the Walter Reed staging classification for HIV infection. J AIDS 1988;1(4):367-374.
36. Hopewell PC. Diagnosis of *Pneumocystis carinii* pneumonia. Infect Dis Clin North Am 1988;2:409-418.
37. Nebupent product monograph. Deerfield IL: Fujisawa, 1990.
38. Riley RL. Airborne infection. Am J Med 1974;57:466-475.
39. American Society of Heating, Refrigerating, and Air Conditioning Engineers. 1987 ASHRAE handbook: heating, ventilating, and air-conditioning systems and applications. Atlanta: ASHRAE, 1987;23:1-12.
40. Riley RL, Nardell EA. Clearing the air: the theory and application of UV air disinfection. Am Rev Respir Dis 1989;139:1286-1294.
41. Wells WF, Wells MW, Wilder TS. The environmental control of epidemic contagion: I. An epidemiologic study of radiant disinfection of air in days schools. Am J Hygiene 1942;35:97-121.
42. Pippin DJ, Verderame RA, Weber KK. Efficacy of face masks in preventing inhalation of airborne contaminants. J Oral Maxillofac Surg 1987;45:319-323.

Toxicology of Antimicrobial Aerosols: A Review of Aerosolized Ribavirin and Pentamidine

Hetty Waskin MD MSPH

Introduction

Inhaled pharmaceutical aerosols have been developed to optimize the delivery of a drug to the site of activity while minimizing or delaying systemic consequences of therapy. Aerosol delivery of drugs allows for higher drug dosage, prolonged duration of therapy, or the administration of drugs considered too toxic to be given systemically. The potential for toxicity of these agents may thus be considerable. Knowledge regarding the potential long-term toxicity of inhaled pharmaceutical aerosols remains incomplete, with much yet to be learned.

To understand the potential toxicity of inhaled aerosols, several general principles are useful. First, consider the toxicity of the drug when given by any route. Second, understand the long-term effects of the drug if given chronically. Third, delineate the eventual fate of the aerosol with regard to metabolism, systemic absorption, and rapidity of elimination from the body.

A drug that has minimal toxicity when given systemically generally has little toxicity when given as an aerosol, even if given in high doses or at frequent intervals (for example, beta-lactam antibiotics given by aerosol as adjunctive therapy for cystic fibrosis).

Dr Waskin is Assistant Professor of Medicine, Division of Infectious Diseases and International Health, Duke University Medical Center, Durham, North Carolina.

A version of this paper was presented by Dr Waskin during the Consensus Conference on Aerosol Delivery, sponsored by the American Association for Respiratory Care, The American Respiratory Care Foundation, and the journal RESPIRATORY CARE, January 10-12, 1991, in Cancun, Mexico.

Reprints: Hetty Waskin MD, Duke University Medical Center, Box 3110, Durham NC 27710.

Drugs with significant toxicity when given systemically may have little toxicity when given as aerosols if the drug is poorly absorbed from the respiratory tract and rapidly eliminated from the body. One example of this would be topical corticosteroids (such as triamcinolone acetonide) given via inhaler.

Finally, aerosolized drugs of concern from a toxicologic point of view are those remaining in the body for a prolonged period of time and associated with cumulative organ damage. Two antimicrobials recently developed for aerosol therapy, ribavirin and pentamidine, fit this category.

A variety of antimicrobial agents have been investigated as aerosols for the treatment of pulmonary infections. Aerosol delivery of an antimicrobial allows targeted therapy to be optimized at the site of infection, with much higher drug levels achieved in bronchoalveolar secretions and within pulmonary macrophages, the primary host defense against lung pathogens. Antimicrobials that have been given as aerosols include beta-lactams, aminoglycosides, amphotericin, pentamidine, and ribavirin. Recently, investigators have begun to study the potential for immunomodulators such as gamma interferon and vaccines to be administered as aerosols. This review will focus on the two antimicrobial aerosols currently in widespread use: ribavirin for the treatment of acute respiratory syncytial virus (RSV) infection and pentamidine for the prevention and treatment of *Pneumocystis carinii* pneumonia (PCP) in the immunocompromised host.

Ribavirin

Spectrum of Usage

Ribavirin is a synthetic nucleoside analogue related to guanosine and is licensed in the United

States for the short-term treatment of RSV infection.[1] In vitro, ribavirin has demonstrated diverse antiviral activity, with inhibition of RNA viruses, including RSV, influenza A and B, hepatitis A and B, measles, mumps, Lassa fever, Rift valley fever, Hantaan virus, and the human immunodeficiency virus (HIV).[2,3] In vitro, ribavirin also inhibits DNA viruses, including herpes simplex Types 1 and 2, cytomegalovirus, adenovirus, and vaccinia.[2-4] In vivo, ribavirin has demonstrated clinical utility in the treatment of acute RSV infections in infants, children,[5] and immunocompromised hosts,[6] Lassa fever virus, Rift Valley fever virus, and Hantaan virus.[7-11] Clinical trials have also been conducted to evaluate the efficacy of ribavirin against influenza A and B, genital herpes simplex infections, hepatitis C, and HIV infection;[4,12-14] however, clinical efficacy has not been verified. At high concentrations in vitro (5-12.5 μg/mL), ribavirin may inhibit some gram-negative bacteria, including *Pseudomonas* and *Brucella* species. In vitro, antifungal inhibition has been seen at concentrations > 500 μg/mL.[15-18]

Mechanism of Action

The mechanism of action of ribavirin is incompletely understood and appears to be multifaceted, in part explaining the drug's diverse antiviral activity. Ribavirin is actively transported intracellularly via a nucleoside transport mechanism. Intracellular concentrations thus may be manyfold greater than plasma concentrations, and the drug persists for many weeks in certain cells, such as red blood cells. Once intracellular, the drug undergoes phosphorylation; the active antiviral compounds are the mono- and triphosphates.[19] Ribavirin 5'-triphosphate inhibits viral RNA polymerase, inhibits the phosphorylation of thymidine, and inhibits viral coating. Both host- and viral-RNA synthesis may be inhibited (the latter to a greater degree), and the degree of inhibitory activity varies among different host cells. The inhibitory concentration (IC50) of the drug varies from 3-30 μg/mL for RSV, from 3-8 μg/mL for influenza A, and from 10-100 μg/mL for HIV.[17,20]

Method of Delivery

Systemic absorption of ribavirin occurs if the drug is given by nasal or oral inhalation, enterally, or intravenously. No data are available regarding cutaneous or mucocutaneous absorption. The amount of drug delivered when the drug is given as an aerosol depends upon the concentration of the drug solution and the duration of therapy. As an aerosol, ribavirin is licensed to be given only when nebulized in a Small Particle Aerosol Generator (SPAG).[21] This nebulizer system produces respirable particles with a mass median aerodynamic diameter (MMAD) of 1.3 μm, with 95% of the particles having a mass diameter < 5 μm.[22] Because infants and children may be unable to utilize hand-held nebulizers, the SPAG is designed to nebulize ribavirin into an oxygen hood, oxygen tent, or face mask. Given this type of open nebulization system, it is apparent that aerosolization of the drug may result in the release of ribavirin into the patient's room; the implications of this will be discussed further in this article. Administration of ribavirin in the intubated patient must be undertaken cautiously. Although nebulized ribavirin has been administered via an endotracheal tube, precipitation of the solution may occur and interfere with mechanical ventilation of the patient.[23]

Concentration of Drug

With nebulization of ribavirin, peak plasma levels occur at the end of inhalation. Over time, intracellular accumulation of the drug occurs, with a very long terminal half-life detected within cells.[24,25] When ribavirin was given by aerosol over 8 hours for 3 days, the peak plasma level was 1.1 μg/mL (range 0.45-2.18 μg/mL); when it was given over 20 hours for 5 days, the peak plasma level was 1.7 μg/mL (range 0.38-3.58 μg/mL). Respiratory secretion levels were 100-fold greater than plasma levels: When ribavirin was given over 3 days, respiratory levels ranged from 250-1,925 μg/mL; and when it was given over 5 days, respiratory levels ranged from 313-28,250 μg/mL.[18,26] Oral plasma levels are slightly less than those achieved via the aerosol route.[27] After 1 gram of ribavirin was administered orally, plasma levels were 0.43-1.33 μg/mL. When ribavirin is inhaled, it is likely that some drug is swallowed with oropharyngeal secretions while additional drug is deposited in the respiratory tract.

Distribution of Drug

Following inhalation, ribavirin is deposited in the respiratory tract, and it subsequently redistributes into the circulation, with eventual accumulation in red blood cells.[28] There is progressive accumulation in red blood cells via an active transport mechanism. Intracellular red blood cell levels of ribavirin are 100-fold greater than plasma levels of the drug. Following a single dose of ribavirin aerosol, peak red blood cell levels are not seen until 4 days after inhalation, with a terminal half-life of 40 days. This prolonged tissue half-life must be considered when patients are evaluated for possible hematologic toxicity.

Elimination of Drug

Approximately 30-55% of a dose of ribavirin is excreted in the urine within 72 hours; an additional 15% of the dose is excreted in the feces.[29,30] Residual ribavirin remains sequestered in red blood cells for several weeks. Ribavirin does not appear to be exhaled from the respiratory tract to a significant degree. The drug has been shown to be excreted in the breast milk of various animals.[17] It is not removed by hemodialysis.[31]

Intracellular Host Effects

Although virucidal, ribavirin and its triphosphate derivative also inhibit cellular DNA synthesis.[17,32] This cytotoxic effect occurs at drug levels 100- to 200-fold greater than virustatic levels. Ribavirin has been found to inhibit cellular division, DNA and RNA synthesis, and protein synthesis of mammalian cells. Perhaps because of this inhibition, ribavirin and its derivatives have demonstrated some antitumor activity, but to date the drug has limited clinical utility in the treatment of malignancy.[33,34]

At low concentrations, ribavirin may stimulate viral-specific antibody by stimulating T-lymphocyte function. At higher concentrations, however, a decrease in cellular immune response has been noted.[35-38] Administration of ribavirin in high concentrations to animals for a prolonged period may result in atrophy of the thymus, spleen, and lymph nodes.[17] Ribavirin may also inhibit release of RSV-specific IgE and histamine.[39] Because of the potential T-cell immunosuppressive effects of ribavirin, some investigators have proposed the combined use of ribavirin and cyclosporine in transplantation to prevent rejection of donor organs.

Adverse Effects in Patients

The principal adverse effects of aerosolized ribavirin when given in the treatment of acute RSV infections are respiratory, cardiovascular, hematologic, and mucocutaneous reactions.

The aerosolization of ribavirin has resulted in the acute worsening of asthma or chronic obstructive lung disease.[18,40] Deterioration of pulmonary function, chest pain, and dyspnea have been reported in adults treated with ribavirin.[14,18,41] Pneumothorax and bacterial pneumonia have also been reported following ribavirin use. The chronic respiratory effects of aerosol ribavirin when it was given to ferrets at a dose of 60 mg/kg of body weight for 10-30 days, included inflammatory and emphysematous changes in the lungs.[42]

Cardiovascular instability has also been reported in persons treated with ribavirin.[43,44] Cardiac sequelae included hypotension, asystole, and cardiac glycoside intoxication. When given chronically to rodents or monkeys, ribavirin induced cardiac lesions.[45]

Given the accumulation of ribavirin in red blood cells, it is not surprising that hemolytic anemia, reticulocytosis, and suppression of erythropoiesis are common side effects of ribavirin when the drug is administered orally or parenterally.[19,46] Hematologic adverse effects have not been reported with short-term aerosol use; but, continued surveillance of hematologic function following a course of aerosol therapy has been infrequent. Further data are needed regarding long-term effects of ribavirin on hematologic parameters. When ribavirin is given orally or parenterally, the likelihood of anemia appears to be dose- and duration-dependent, and it is generally reversible over time.[28,36]

Other adverse effects reported in a minority of patients include rash, eyelid erythema, conjunctivitis, and changes in liver enzymes.[7,38,44,47]

Carcinogenicity and Mutagenicity

Because of the potential for long-term intracellular accumulation of ribavirin, a thorough understanding

of the drug's potential as a mutagenic or teratogenic compound is important in the assessment of potential risk. Ribavirin has been carcinogenic and tumorigenic when studied in vitro and in animals.[15,17,18,48] The drug induces cell transformation of the Balb/C 3T3 mammalian cell line. Chronic feeding of ribavirin to rats at a dose of 16-60 mg/kg of body weight caused benign tumors of the breast, pancreas, central nervous system, and adrenal gland. Ribavirin was mutagenic to the L5178Y mammalian cell culture; however, Ames testing and lethal mouse assay were negative.[15,48]

Fertility and Pregnancy

Ribavirin has caused testicular lesions in rats when given in doses as low as 16 mg/kg of body weight.[49] However, fertility function has been inadequately studied; as yet, there is no information regarding the potential testicular effects of lower doses and no information regarding ribavirin's effects on ovulatory function or female fertility.

The potential effect of ribavirin on pregnancy is of major concern. This is because the drug has been shown to be teratogenic and/or embryocidal in most animal species that have been studied. Teratogenicity was seen when hamsters were given a single dose of 2.5 mg/kg of body weight, when rats were given daily doses of 10-90 mg/kg of body weight, and when rabbits were given daily doses of 1 mg/kg of body weight.[50] Malformations of the fetus included abnormalities of the skull, central nervous system, skin, palate, jaw, skeleton, and gastrointestinal tract; increased fetal wastage was also noted.[51] One study in baboons did not demonstrate teratogenicity when ribavirin was given in doses up to 100 mg/kg of body weight.[17] Ribavirin has not been linked to fetal abnormalities in humans; however, given the wide spectrum of teratogenic potential in most animal species, avoidance of ribavirin prior to pregnancy, during pregnancy, and during lactation is warranted.

Adverse Effects in Health-Care Workers

The potential for chronic toxicity from ribavirin in exposed health-care workers is unknown. Research on this subject is evolving, and an assessment of the degree of health-care workers' exposure to ribavirin remains incomplete.[52,53]

Few acute side effects have been reported by health-care workers. Ribavirin has been reported to precipitate on contact lenses, and health-care workers exposed to the drug should be so advised.[54] Such ocular precipitation has resulted in conjunctival irritation; however, long-term ocular effects have not yet been noted.

Because the long-term consequences of exposure to aerosolized ribavirin are unknown, investigators are beginning to measure the degree of drug contact experienced by health-care workers.[26] Air has been sampled at various sites in patients' rooms.[55] The environmental concentrations of the drug have been found to be 579 $\mu g/m^3$ when the drug was given via tracheostomy, 161 $\mu g/m^3$ when given via oxygen tent, 143 $\mu g/m^3$ when given via hood, and 6 $\mu g/m^3$ when given via ventilator.[56,57] Long-term studies of health-care workers exposed to the drug have not yet been completed. Because ribavirin accumulates in red blood cells and is excreted in the urine, it is reasonable to monitor red blood cell and urinary ribavirin levels in health-care workers to assess exposure. Two studies have conducted short-term sampling, and ribavirin in a low concentration (0.44 $\mu g/mL$) has been detected in the blood of one health-care worker directly involved in the care of a patient who received ribavirin via an oxygen tent.[53,57]

In attempts to minimize the release of ribavirin aerosol into the air space adjacent to patients, several scavenger systems have been proposed and implemented by investigators.[58,59] Such systems generally involve a containment area around the patient who is receiving aerosolized ribavirin and/or an exhaust system to capture drug released into the environment.[58] One such system resulted in no detected levels of ribavirin released into areas adjacent to the treatment site.[59] Another approach to minimizing the passive exposure of health-care workers to the drug involves the use of personal protective equipment such as gowns, gloves, masks, and/or personal respirators. Surgical masks are not sufficient protection; to be effective, masks must filter out ribavirin particles as small as 1 μm. Current health-care worker guidelines published by the Centers for Disease Control include advising health-care workers and visitors who are or may become pregnant of the potential risks of exposure to ribavirin, and developing procedures to minimize employee exposure to the drug.[53]

Pentamidine

Spectrum of Activity

Aerosolized pentamidine has been administered for the prevention and treatment of *Pneumocystis carinii* pneumonia (PCP) only since 1986; however, pentamidine has been given systemically for more than 50 years to treat various protozoal infections.[60,61] Because of the extensive experience with systemic pentamidine, much of the understanding of aerosolized pentamidine can be extrapolated from data regarding the drug's systemic use.

Pentamidine is an aromatic diamidine that was first synthesized in 1937 as a potential therapy for diabetes mellitus.[60] However, it was not used in the treatment of diabetes because its hypoglycemic activity was unpredictable. Subsequently, in the 1940s, investigators documented the efficacy of intramuscular pentamidine to treat and prevent African sleeping sickness (African trypanosomiasis), and the drug was used in several thousand patients for this purpose.[61] Investigators found that a single dose of 300 mg of pentamidine given intramuscularly would protect gold miners against trypanosomiasis for more than 6 months. This prophylactic effect was due to the drug's long tissue half-life. Now, in the 1990s, aerosolized pentamidine is widely used as a prophylaxis to protect immunocompromised individuals against infection with PCP.

Pentamidine is effective against a variety of protozoal infections, including trypanosomiasis, leishmaniasis, pneumocystosis, and babesiosis,[62] and it has been used clinically to treat these infections. Pentamidine is active in vitro against some bacteria and fungi, including *Escherichia coli*, *Staphylococcus*, *Candida*, and *Cryptococcus* species. Weak antiviral activity has also been noted; potential activity against the HIV is unknown.

The drug has been used, with limited efficacy, to treat several neoplastic conditions, including multiple myeloma and islet cell carcinoma; it is not recommended as a chemotherapeutic agent. Pentamidine and related diamidines have demonstrated anti-inflammatory effects;[63] further investigation of this property of the drug is in progress.

Mechanism of Action

The precise mechanism of action of pentamidine as an antiprotozoal drug is not fully understood. Pentamidine interferes with RNA and DNA synthesis by binding to nucleic acids.[64] It inhibits oxidative phosphorylation and disrupts mitochondrial kinetoplasts.[62] Pentamidine may also interfere with folate transformation.[62] Perhaps because of the multifaceted action demonstrated in vitro, the drug is 'cidal' to *Pneumocystic carinii*, and no resistance of pneumocystis to pentamidine has been documented.

In 1986, aerosolized pentamidine was reported to be effective in preventing PCP in immunosuppressed rodents.[65] Aerosolized pentamidine quickly gained widespread popularity in the prevention of PCP among persons infected with the HIV. PCP continues to be the most common opportunistic infection in such persons. As many as 50-60% of HIV-infected persons will develop PCP as their AIDS-defining illness, and ultimately 65-80% of immunosuppressed HIV-infected persons will develop PCP.[66,67] Aerosolized pentamidine is approved by the Food and Drug Administration (FDA) for use in the United States to prevent recurrence of PCP following its first episode (secondary prophylaxis) or to prevent occurrence of PCP in HIV-infected persons with a CD-4 lymphocyte count < 200 or a CD-4 lymphocyte percentage < 20% (primary prophylaxis).

Pharmacokinetic Profile

Pentamidine is absorbed if given intravenously, intramuscularly, or as an aerosol, but not if given orally.[68,69] Once given parenterally, it is detected only transiently in plasma; peak levels of 209 and 612 ng/mL are seen 40 minutes after intramuscular injection and at the completion of intravenous infusion, respectively.[68] Following the brief plasma peak, the drug distributes to the liver, kidneys, adrenals, spleen, lung, and pancreas.[70] Pentamidine binds extensively to tissues, is stored in the body for months, and is slowly excreted. Approximately 25% of the drug is excreted in the feces; the rest is excreted in the urine.[68,69] A single dose of pentamidine given intramuscularly has been noted to result in detectable pentamidine excretion in the

urine for 270 days.[61] Because of tissue binding and slow excretion, plasma levels of the drug are not affected by peritoneal dialysis, hemodialysis, or renal insufficiency.[71]

When the drug is given as an aerosol, pentamidine levels in the lung are 5- to 10-fold greater than when the drug is given parenterally.[68,69] At the same time, plasma levels are less than 5% of those seen with parenteral administration.[68,69] Thus, the potential for systemic accumulation of the drug is greatly reduced when pentamidine is given as an aerosol. When aerosolized, it initially binds to lung tissue, then is slowly absorbed into the systemic circulation, redistributes to various body tissues, and is eventually excreted in the urine and feces. Following prolonged aerosol administration, systemic accumulation of pentamidine can and does occur; this accumulation may eventually result in systemic toxicity.

In the past, investigators believed that pentamidine was excreted unchanged in the urine. However, recent studies have documented significant metabolism of the drug to hydroxyl products.[72] Currently, researchers are studying the metabolic fate of pentamidine. Until further information is available regarding the metabolism of the drug, the clinical interpretation of assaying drug levels in urine and tissues will be limited.

Administration of Aerosolized Pentamidine

Aerosolization of pentamidine is an attractive alternate mode of administration because the site of infection of PCP is the alveolar space, and systemic dissemination of pneumocystis is rare. Various nebulizer systems have been used to administer pentamidine. Early clinical trials demonstrated initial effectiveness of aerosol therapy but subsequent relapse; relapse was likely due to the nebulization of particles too large to reach the alveoli. Particles $< 3\ \mu m$ in size are most appropriate to assure parenchymal deposition and to reduce airway complications, such as cough.

In the United States, aerosolized pentamidine is currently FDA-approved to be given via the Respirgard II nebulizer at a dose of 300 mg in 6 mL of sterile water once a month.[73] In Canada, the FISONeb ultrasonic nebulizer system is approved for a 60-mg dose of pentamidine twice a month.[74] Nebulizer systems should be compared with caution, because the patient characteristics in various clinical trials can differ with respect to the degree of immunosuppression and the use of other drugs, such as zidovudine. The amount of deposition of pentamidine may also vary, depending upon the patient's breathing pattern, the degree of cooperation, fatigue, and anatomic considerations.[75] Complete nebulization of the drug is important when pentamidine is given via the Respirgard II nebulizer because the drug becomes concentrated during the second half of the treatment period. The amount of drug delivered is much less than the amount placed in the nebulizer; the Respirgard II system delivers 10-15% of a 300-mg dose (unpublished data).

Relapse of PCP

Pentamidine aerosol prevents PCP in immunocompromised persons; however, with prolonged duration of therapy, PCP relapse may occur. Because the efficacy of pentamidine aerosol depends upon the drug's reaching the site of infection, any condition that may impair uniform aerosol delivery may increase the likelihood of relapse. Patients with pulmonary pathology such as Kaposi's sarcoma, pneumothorax, concurrent pneumonia, or significant bronchospasm with drug nebulization are at increased risk for PCP relapse.[73,76] The current estimate of the rate of PCP relapse is 10-15% per year among HIV-infected persons receiving aerosolized pentamidine. PCP relapse may appear as focal upper-lobe disease or concurrent with pneumothorax.[76,77] Bronchoalveolar lavage is less sensitive in detecting PCP in patients on pentamidine aerosol therapy; transbronchial biopsy should be undertaken in such patients.

Relapse of pneumocystis in sites other than the lungs has been reported by numerous investigators.[78] Extrapulmonary pneumocystosis may occur in the choroid/retina, auditory canal, liver, lymph nodes, or as diffuse disease.[78] Extrapulmonary relapse is not unexpected, because systemic drug levels are much lower than pulmonary levels.

Adverse Effects in Patients

Adverse effects are common when pentamidine is given parenterally, occurring in more than 50%

of patients.[79] Reported toxicities have included azotemia (23%), hypotension (14%), dysglycemia (14%), leukopenia (8%), and hepatic dysfunction (5%). Because pentamidine is a derivative of drugs with known hypoglycemic activity, it is not surprising that dysglycemia is a common side effect of parenteral pentamidine therapy. Prolonged administration of pentamidine results in a cumulative cytotoxic effect on pancreatic beta cells, with inappropriate insulin release. Sudden hypoglycemia may occur, and may be followed by permanent insulin-dependent diabetes mellitus. Both azotemia and dysglycemia are dose-dependent, occurring with increased frequency in patients who receive prolonged or recurrent parenteral therapy.[79]

Pancreatitis has also occurred in patients receiving parenteral pentamidine,[80] although the incidence of pancreatitis is much lower than that of dysglycemia. Pancreatitis may occur suddenly and has been severe or fatal in some cases.[80] Cofactors such as cytomegalovirus infection or concurrent administration of other drugs such as dideoxyinosine may contribute to pancreatitis. Less frequent adverse effects with parenteral pentamidine include hyperkalemia, sterile abscess with intramuscular administration of the drug, phlebitis, nausea, hypocalcemia, and seizures.[62,79]

Systemic toxicity is much less common when pentamidine is given by aerosol rather than parenterally. However, because pentamidine deposited in the lung is eventually absorbed, the drug persists in the body for months prior to renal excretion. Thus, chronic exposure to the aerosolized drug will lead to drug accumulation and may result in toxicity. Side effects of pentamidine aerosol have included conjunctivitis, rash, neutropenia, pancreatitis, renal insufficiency, dysglycemia (both hypoglycemia and diabetes), and local effects of the drug on the respiratory tract.[81-85]

When pentamidine is nebulized, the drug first impacts on the hypopharynx, trachea, and bronchial tree prior to reaching its target, the alveolar space. Particles > 4 μm in diameter are nonrespirable and deposit on the back of the throat. These particles, by virtue of their size, are likely to cause cough and irritation. In addition, pentamidine itself is a bronchial irritant. As a consequence, cough and bronchial irritation are common when pentamidine aerosol is administered. In two large-scale trials using the Respirgard II nebulizer[73] or the FISONeb nebulizer,[74] coughing occurred in 36 and 38% of the participants, respectively, and bronchospasm occurred in 11 and 13%. Pretreatment with albuterol was subsequently given to 14%[73] and 25%[74] of the study patients, and this resulted in successful continuation of pentamidine therapy in all but 1% of the participants.

Transient changes in FEV_1 have been reported with pentamidine aerosol. Long-term deterioration of pulmonary function has not been reported; conversely, pulmonary function (particularly D_{LCO}), improves in persons receiving secondary prophylaxis, mostly due to resolution of pre-existing PCP. Other reported respiratory effects have been dry mouth, metallic taste, rhinitis, pharyngitis, laryngitis, dyspnea, and chest pain.[62] One case of fatal pulmonary hemorrhage has been reported following bronchoscopy of a patient on chronic pentamidine aerosol therapy.[86]

Fertility and Pregnancy

Limited data are available regarding the potential effects of pentamidine on the fetus. Pentamidine studied in vitro is transported across the isolated placenta.[87] When pentamidine was given to rodents in a dose of 1 to 8 mg/kg of body weight, a mild increase in post-implantation loss occurred, and there was delayed ossification of the fetus.[88] No other fetal abnormalities have been reported. Early studies of pentamidine given to treat African sleeping sickness reported no ill effects on pregnant women; however, detailed clinical data were not obtained. No data are available regarding dose effects on spermatogenesis or ovarian development.

Carcinogenicity and Mutagenicity

Most in-vitro assays, including the Ames test and cytogenic assays using human lymphocyte cultures, have been negative for mutagenic potential.[62] Weak mutagenic activity in mouse lymphoma cells was seen at drug levels of 62.5-500 μg/mL. Thus, to date, the carcinogenic potential of pentamidine appears minimal.

Health-Care Worker Exposure

Occupational concerns regarding the use of pentamidine aerosol include, first, the consequences of passive exposure to the drug, and, secondly, the

possible transmission of respiratory pathogens exhaled or coughed out by the patient.[89] The amount of pentamidine released into the environment depends upon the nebulizer apparatus; the presence of expiratory filters to capture exhaled drug; continuing nebulization of drug into the air if the mouthpiece is removed for coughing, talking, rest, or other interruptions of treatment; and the ventilation of the treatment room.

In an optimal setting, with appropriate room ventilation, occupational exposure to pentamidine should be minimal. However, optimal room ventilation may not exist. One study measured air samples in a room dedicated to aerosol treatments and estimated the daily dose to a health-care worker to be 2.2×10^{-5} mg of drug.[89] And one preliminary study has reported detecting low levels of pentamidine in the urine of 5 of 14 health-care workers chronically exposed to the drug.[90] Transient conjunctivitis and bronchospasm have also been reported by health-care workers in contact with pentamidine aerosol (unpublished data). Given these findings and the potential for long-term persistence of inhaled pentamidine in the body, ventilation guidelines developed by the Centers for Disease Control should be followed.[91] These guidelines were developed to minimize the transmission of tuberculosis and other respiratory pathogens exhaled by HIV-infected patients, and they may also reduce environmental release of aerosolized pentamidine. The guidelines include the use of single-patient treatment rooms or booths, six or more room-air exchanges per hour, non-recirculation of treatment-room air, and maintaining negative air pressure in the treatment area with respect to adjacent care areas.

Summary

Ribavirin and pentamidine are both effective in the treatment or prevention of pulmonary infection. This efficacy is achieved by targeting drug delivery to the site of infection. Aerosolization of these two antimicrobials allows much higher drug levels to be achieved in bronchoalveolar secretions than would result if the drugs were given systemically. Eventual systemic absorption of each drug does occur, however, and because of intracellular transport or tissue binding, prolonged drug concentrations remain in the host prior to elimination of ribavirin or pentamidine from the body.

Toxic effects may result from the administration of either ribavirin or pentamidine. Significant adverse effects reported with the use of ribavirin include anemia if the drug is given orally or parenterally, and cardiac instability or worsening respiratory function if it is given as an aerosol. Ribavirin has been teratogenic in most animal species that have been studied. Adverse effects reported with pentamidine aerosol reflect the toxicities that may occur when it is given parenterally, albeit at a much lower incidence. These adverse effects include azotemia, dysglycemia, pancreatitis, and leukopenia. Pentamidine aerosol may irritate the bronchial tree and cause cough or bronchospasm; pretreatment with bronchodilators can control bronchial hyperreactivity.

The potential for health-care-worker exposure to either aerosolized ribavirin or pentamidine occurs due to release of drug into the environment. Further research is needed to assess the potential significance of chronic exposure to these drugs. Steps to minimize health-care-worker exposure are appropriate, and include the design of treatment areas to minimize passive exposure,[71] and the use of masks and protective clothing as recommended by the Centers for Disease Control.[91]

REFERENCES

1. Food and Drug Administration. Ribavirin aerosol approved for severe cases of RSV in infants and young children. FDA Drug Bull 1986;16:7.
2. Sidwell RW, Robin RK, Hillard W. Ribavirin: an antiviral agent. Pharmacol Ther 1979;6:123-146.
3. Sidwell RW, Huffman JH, Khare GP, Allen LB, Witkowski JT, Robins RK. Broad-spectrum antiviral activity of Virazole. Science 1972;177:705-706.
4. Palmieri G, Ambrosi G, Ferraro G, Agrati AM, Palazzini E. Clinical and immunological evaluation of oral ribavirin administration in recurrent herpes simplex infections. J Int Med Res 1987;15:264-275.
5. Groothuis JR, Woodin KA, Katz R, Robertson AD, McBride JT, Hall CB, et al. Early ribavirin treatment of respiratory syncytial viral infection in high-risk children. J Pediatr 1990;117:792-798.
6. Englund JA, Sullivan CJ, Jordan MC, Dehner LP, Vercellotti GM, Balfour HH Jr. Respiratory syncytial virus infection in immunocompromised adults. Ann Intern Med 1988;109:203-208.
7. McCormick JB, King IJ, Webb PA, Scribner CL, Craven RB, Johnson KM, et al. Lassa fever: effective therapy with ribavirin. N Engl J Med 1986;314:20-26.

8. Taber LH, Knight V, Gilbert BE, McClurg HW, Wilson SZ, Norton HJ, et al. Ribavirin aerosol treatment of bronchiolitis associated with respiratory syncytial virus infection in infants. Pediatrics 1983;72:613-618.
9. Hall CB, McBride JT, Walsh EE, Bell DM, Gala CL, Hildreth S, et al. Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. N Engl J Med 1983;308:1443-1447.
10. Centers for Disease Control. Management of patients with suspected viral hemorrhagic fever. MMWR 1988; 37(S-3):1-6.
11. Huggins JW. Prospects for treatment of viral hemorrhagic fevers with ribavirin, a broad-spectrum antiviral drug. Rev Infect Dis 1989;11(4, Suppl):750S-761S.
12. Reichard O, Andersson J, Schvarcz R, Weiland O. Ribavirin treatment for chronic hepatitis C. Lancet 1991;337:1058-1061.
13. Roberts RB, Dickinson GM, Heseltine PN, Leedom JM, Mansell PW, Rodriguez S, et al. The Ribavirin-LAS Collaborative Group. A multicenter clinical trial of oral ribavirin in HIV-infected patients with lymphadenopathy. J AIDS 1990;3:884-892.
14. Aschan J, Ringden O, Ljungman P, Andersson J, Lewensohn-Fuchs I, Forsgren M. Influenza B in transplant patients. Scand J Infect Dis 1989;21:349-350.
15. Anonymous. Ribavirin. In: McEvoy GK, ed. American Hospital Formulary Service drug information. Bethesda MD: American Society of Hospital Pharmacists Inc, 1990:372-379.
16. Fernandez H, Banks G, Smith R. Ribavirin: a clinical overview. Eur J Epidemiol 1986;2:1-14.
17. Smith RA, Kirkpatrick W, eds. Ribavirin: a broad-spectrum antiviral agent. New York: Academic Press, 1980.
18. Smith RA, Knight V, Smith JAD, eds. Clinical application of ribavirin. New York: Academic Press, 1984.
19. Smee DF, Matthews TR. Metabolism of ribavirin in respiratory syncytial virus-infected and uninfected cells. Antimicrob Agents Chemother 1986;30:117-121.
20. Patterson JL, Fernand-Larsson R. Molecular mechanisms of action of ribavirin. Rev Infect Dis 1990;6:1139-1146.
21. ICN Pharmaceuticals Inc. Virazole (ribavirin): prescribing information. Costa Mesa CA: ICN Pharmaceuticals Inc, 1987.
22. Newth CJ, Clark AR. In vitro performance of the small particle aerosol generator (SPAG-2). Pediatr Pulmonol 1989;7:183-188.
23. Demers RR, Parker J, Frankel LR, Smith DW. Administration of ribavirin to neonatal and pediatric patients during mechanical ventilation. Respir Care 1986;31:1188-1195.
24. Knight V, Yu CP, Gilbert BE, Divine GW. Estimating the dosage of ribavirin aerosol according to age and other variables. J Infect Dis 1988;158:443-448.
25. Englund JA, Piedra PA, Jefferson LS, Wilson SZ, Taber LH, Gilbert BE. High-dose, short-duration ribavirin aerosol therapy in children with suspected respiratory syncytial virus infection. J Pediatr 1990;117:313-320.
26. Gladu JM, Ecobichon DJ. Evaluation of exposure of health care personnel to ribavirin. J Toxicol Environ Health 1989;28:1-12.
27. Laskin OL, Longstreth JA, Hart CC, Scavuzzo D, Kalman CM, Connor JD, et al. Ribavirin deposition in high-risk patients for acquired immunodeficiency syndrome. Clin Pharmacol Ther 1987;41:546-555.
28. Canonico PG, Kastello MD, Spears CT, Brown JR, Jackson EA, Jenkins DE. Effects of ribavirin on red blood cells. Toxicol Appl Pharmacol 1984;74:155-162.
29. Ferrera EA, Oishi JS, Sannemacher RW, Stephen EL. Plasma disappearance, urine excretion, and tissue distribution of ribavirin in rats and rhesus monkeys. Antimicrob Agents Chemother 1981;19:1042-1049.
30. Paroni R, Del Puppo M, Borghi C, Sirtori CR, Galli M. Pharmacokinetics of ribavirin and urinary excretion of the major metabolite in normal volunteers. Int J Clin Pharm Ther Toxicol 1989;27:302-307.
31. Kramer TH, Gaar GG, Ray CG, Minnich L, Copeland JG, Connor JD. Hemodialysis clearance of intravenously administered ribavirin. Antimicrob Agents Chemother 1990;34:489-490.
32. Yamada Y, Goto H, Yoshino M, Ogasawara N. IMP dehydrogenase and action of antimetabolites in human cultured blast cells. Biochim Biophys Acta 1990;1051:209-214.
33. Tricot G, Jayaram HN, Weber G, Hoffman R. Tiazofurin: biological effects and clinical uses. Int J Cell Cloning 1990;8:161-170.
34. Kini GD, Robins RK, Avery TL. Synthesis and antitumor activity of ribavirin imidates: a new facile synthesis of ribavirin amidine (1-beta-D-ribofuranosyl 1-1,2,4-triazole-3-carboxamine hydrochloride). J Med Chem 1989;32:1447-1449.
35. Powers CN, Peavy DL, Knight V. Selective inhibition of functional lymphocyte subpopulations by ribavirin. Antimicrob Agents Chemother 1982;22:108-114.
36. Canonico PG. Efficacy, toxicology, and clinical applications of ribavirin against virulent RNA viral infections. Antiviral Res 1985;(1, Suppl):75-81.
37. Peavy DL, Koff WC, Hyman DS. Inhibition of lymphocyte proliferative responses by ribavirin. Infect Immun 1980;29:583-589.
38. Marquardt DL, Gruber HE, Walker LL. Ribavirin inhibits mast cell mediator release. J Pharmacol Exp Ther 1987;240:145-149.
39. Rosner IK, Welliver RC, Edelson PJ, Geraci-Ciardullo K, Sun M. Effect of ribavirin therapy on respiratory syncytial virus-specific IgE and IgA response after infection. J Infect Dis 1987;155:1043-1047.
40. Cosgrove M, Jenkins HR, Rowlandson PH, Gray OP. Idiosyncratic reaction to nebulised ribavirin in an artificially ventilated neonate (letter). J Infect 1989;19:85-87.

41. Janai H. Adverse drug reactions: United States experience. I. Pediatr Infect Dis J 1990;9(Suppl):115S-116S.
42. Hoffman SH, Staffa JA, Smith RA, Craig DK, Parker G. Inhalation toxicity of ribavirin in suckling ferrets. J Appl Toxicol 1987;7:343-351.
43. Eisenberg J. Hemodynamic alterations in patients treated with ribavirin. Pediatr Infect Dis J 1990;9(Suppl):93S-94S.
44. Martin JT, Kugler JD, Gumbiner CH, Brown JC, Murphy KR, Colombo JL, et al. Refractory congestive heart failure after ribavirin in infants with heart disease and respiratory syncytial virus. Nebr Med J 1990;75:23-26.
45. Janai HK, Marks MI, Zaleska M, Stutman HR. Ribavirin: adverse drug reactions, 1986 to 1988. Pediatr Infect Dis J 1990;9(Suppl):209S-211S.
46. Gilbert BE, Knight V. Biochemistry and clinical applications of ribavirin. Antimicrob Agents Chemother 1986;30:201-205.
47. Rodriquez WJ, Kim HW, Brandt CD. Aerosolized ribavirin in the treatment of patients with respiratory syncytial virus disease. Pediatr Infect Dis J 1987;6:159-163.
48. Rao KP, Rahiman MA. Cytogenic effects of ribavirin on mouse bone marrow. Mutat Res 1989;224:213-218.
49. Marks MI. Adverse drug reactions: United States experience. II. Pediatr Infect Dis J 1990;9(Suppl):117S-118S.
50. Kilham L, Ferm VH. Congenital anomalies induced in hamster embryos with ribavirin. Science 1977;195:413-414.
51. Kochar DM. Effects of exposure to high concentrations of ribavirin in developing embryos. Pediatr Infect Dis J 1990;9(Suppl):8S-90S.
52. Kacmarek RM. Ribavirin and pentamidine aerosols: caregiver beware! (editorial). Respir Care 1990;35:1034-1035.
53. Harrison R, Bellows J, Rempel D, Rudolph L, Kizer KW, Jin A, et al. Centers for Disease Control. Assessing exposures of health care personnel to aerosols of ribavirin, California. MMWR 1988;36:560-563.
54. Diamond SA, Dupuis LL. Contact lens damage due to ribavirin exposure (letter). Drug Intell Clin Pharm 1989;23:428-429.
55. Bradley JS, Connor JD, Compogiannis LS, Eiger LL. Exposure of health care workers to ribavirin during therapy for respiratory syncytial virus infections. Antimicrob Agents Chemother 1990;34:668-670.
56. Harrison R. Reproductive risk assessment with occupational exposure to ribavirin aerosol. Pediatr Infect Dis J 1990;9(Suppl):102S-105S.
57. Rodriquez WJ, Dang Bui RH, Connor JD. Environmental exposure of primary care personnel to ribavirin aerosol when supervising infants with respiratory syncytial virus infection. Antimicrob Agents Chemother 1987;31:1143-1146.
58. Guglielmo BJ, Jacobs RA, Locksley RM. The exposure of health care workers to ribavirin aerosol (letter). JAMA 1989;261:1880-1881.
59. Charney W, Corkery KJ, Kraemer R, Wugofski L. Engineering and administrative controls to contain aerosolized ribavirin: results of simulation and application to one patient. Respir Care 1990;35:1042-1048.
60. Wien R. The pharmacological actions of certain aromatic diamidines possessing trypanocidal activity. Ann Trop Med Parasitol 1943;37:1-18.
61. Van Hoof L, Henrard C, Peel E. Chemoprophylaxis of sleeping sickness by pentamidine. Ann Soc Belge Med Trop 1946;26:371-380.
62. Anonymous. Pentamidine isethionate. In: McEvoy GK, ed. American Hospital Formulary Service drug information. Bethesda MD: American Society of Hospital Pharmacists Inc, 1990:458-466.
63. Rosenthal GJ, Corsini E, Craig WA, Comment CE, Luster MI. Pentamidine: an inhibitor of interleukin-1 that acts via a post-translational event. Toxicol Appl Pharmacol 1991;107:555-561.
64. Perez JM, Navarro-Ranninger MC, Requena JM, Jimenez-Ruiz A, Parrondo E, Craciunescu D, et al. DNA binding properties and antileukemic (L1210) activity of a Pt-pentamidine complex. Chem Biol Interact 1991;77:341-355.
65. Bernard EM, Donnelly HJ, Huang A, Tsang S, Armstrong D. Successful prevention and treatment of experimental *Pneumocystis carinii* pneumonia with aerosol pentamidine (abstract). Paris: 2nd International Conference on AIDS, 1986:54.
66. Centers for Disease Control. Guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for persons infected with the human immunodeficiency virus. MMWR 1989;38(S-5):1-9.
67. Centers for Disease Control. Guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for children infected with human immunodeficiency virus. MMWR 1991;40(RR-2):1-13.
68. Conte JE, Golden JA. Concentrations of aerosolized pentamidine in bronchoalveolar lavage, systemic absorption, and excretion. Antimicrob Agents Chemother 1988;32:1490-1493.
69. Farinotti R, Pascaud MB, Girard PM, Guillot E, Certain A, Trouvin JH. Comparison of tissular disposition of pentamidine mesylate in the rat after aerosol or parenteral administration. J Infect Dis 1989;160:507-512.
70. Donnelly H, Bernard EM, Rothkotter H, Gold JW, Armstrong D. Distribution of pentamidine in patients with AIDS. J Infect Dis 1988;157:985-989.
71. Conte JE. Pharmacokinetics of intravenous pentamidine in patients with normal renal function or receiving hemodialysis. J Infect Dis 1991;163:169-175.
72. Berger BJ, Reddy VV, Le ST, Lombardy RJ, Hall JE, Tidwell RR. Hydroxylation of pentamidine by rat liver microsomes. J Pharmacol Exp Ther 1991;256:883-889.
73. Leoung GS, Feigal DW, Montgomery AB, Corkery K, Wardlaw L, Adams M, et al. Aerosolized pentamidine for prophylaxis against *Pneumocystis carinii* pneumonia: the San Francisco community prophylaxis trial. N Engl J Med 1990;323:769-775.

72. Berger BJ, Reddy VV, Le ST, Lombardy RJ, Hall JE, Tidwell RR. Hydroxylation of pentamidine by rat liver microsomes. J Pharmacol Exp Ther 1991;256:883-889.
73. Leoung GS, Feigal DW, Montgomery AB, Corkery K, Wardlaw L, Adams M, et al. Aerosolized pentamidine for prophylaxis against *Pneumocystis carinii* pneumonia: the San Francisco community prophylaxis trial. N Engl J Med 1990;323:769-775.
74. Murphy RL, Lavelle JP, Allan JD, Gordin FM, Dupliss R, Boswell WL, et al. Aerosol pentamidine prophylaxis following *Pneumocystis carinii* pneumonia in AIDS patients: results of a blinded dose-comparison study using an ultrasonic nebulizer. Am J Med 1991;90:418-426.
75. Baskin MI, Abd AG, Ilowite JS. Regional deposition of aerosolized pentamidine: effects of body position and breathing pattern. Ann Intern Med 1990;113:677-683.
76. Sepkowitz KA, Telzak EE, Gold JW, Bernard EM, Blum S, Carrow M, et al. Pneumothorax in AIDS. Ann Intern Med 1991;114:455-459.
77. Edelstein H, McCage RE. Atypical presentations of *Pneumocystis carinii* pneumonia in patients receiving inhaled pentamidine prophylaxis. Chest 1990;98:1366-1369.
78. Raviglione MC. Extrapulmonary pneumocystosis: the first 50 cases. Rev Infect Dis 1990;12:1127-1138.
79. Waskin H, Stehr-Green JK, Helmick CG, Sattler FR. Risk factors for hypoglycemia associated with pentamidine therapy for Pneumocystis pneumonia. JAMA 1988;260:345-347.
80. Schwartz MS, Cappell MS. Pentamidine associated pancreatitis. Dig Dis Sci 1989;34:1617-1620.
81. Lindley DA, Schleupner CJ. Aerosolized pentamidine and conjunctivitis (letter). Ann Intern Med 1988;109:988.
82. Berger TG, Tappero JW, Leoung GS, Jacobson MA. Aerosolized pentamidine and cutaneous eruptions. Ann Intern Med 1989;110:1035-1036.
83. Murphy RL, Noskin GA, Ehrenpreis ED. Acute pancreatitis associated with aerosolized pentamidine. Am J Med 1990;88:53-55.
84. Chapelon C, Raguin G, DeGennes C. Renal insufficiency with nebulized pentamidine. Lancet 1989;2:1045-1046.
85. Chen JP, Braham RL, Squires KE. Diabetes after aerosolized pentamidine. Ann Intern Med 1991;114:913-914.
86. Miller RF, Semple SJ. Bronchial bleeding with nebulised pentamidine (letter). Lancet 1988;2:1488.
87. Fortunato SJ, Bawdon RE. Determination of pentamidine transfer in the in vitro perfused human cotyledon with high-performance liquid chromatography. Am J Obstet Gynecol 1989;160:759-761.
88. Harstadd TW, Little BB, Bawdon RE. Embryofetal effects of pentamidine isethionate administered to pregnant Sprague-Dawley rats. Am J Obstet Gynecol 1990;163:912-916.
89. Montgomery AB, Corkery KJ, Brunette ER, Leoung GS, Waskin H, Debs RJ. Occupational exposure to aerosolized pentamidine. Chest 1990;98:386-388.
90. Smaldone GC, Vinciguerrra C, Morra L, Marchese J. Urine pentamidine as an indicator of lung pentamidine in patients and health-care workers (abstract). Washington DC: AIDS Clinical Trials Group Meeting, March 1991.
91. Centers for Disease Control. Guidelines for preventing the transmission of tuberculosis in health care settings with special focus on HIV-related issues. MMWR 1990;39(RR-17):1-29.

Propellant Gases in Metered Dose Inhalers: Their Impact on the Global Environment

John R Balmes MD

Introduction

The negative impact of human activities on the global environment has been the subject of much scientific debate over the past several years, and scenarios of the socioeconomic consequences of global warming have received considerable media attention. Concern over the depletion of stratospheric ozone has risen to the point where an almost unprecedented international consensus on an environmental issue has been achieved, and firm steps have been initiated to reduce ozone depletion by a rapid phaseout of chlorofluorocarbon (CFC) production.[1]

The original commercial development of CFCs involved their use as cooling fluids in home refrigerators. Chlorofluorocarbons were either less toxic or less flammable than earlier refrigerants. While their use as refrigerants remains important, CFCs have also found wide application as foam-blowing agents for polystyrene and polyurethane, as industrial solvents and cleaning agents, and as aerosol propellants (here the term "aerosol" is used in its popular sense to refer to self-contained, sprayable products in which the propellant force is provided by liquefied gas). While use of CFCs as aerosol propellants has been banned in North America since 1978, approximately 27% of world CFC consumption was still intended for this use in 1986.[1] One application of CFCs as propellants that was not subject to the 1978 ban was in medical aerosols. The use of CFCs is currently vital to the ability to deliver medications by metered dose inhalers (MDIs).

It is difficult to conceive of the treatment of asthma and chronic obstructive pulmonary disease (COPD) without the ability to deliver beta-agonist bronchodilators, steroids, and sodium cromoglycate by MDI. The introduction of MDIs met with rapid acceptance by both physicians and patients because of their efficacy, safety, and convenience. A widely accepted approach to the stepwise care of asthma starts with inhaled beta agonists and follows with either inhaled steroids or sodium cromoglycate; all of these medications are usually delivered by MDI.[2,3] Sales of MDIs rose rapidly during the 1980s and are projected to continue to rise, especially because new anti-inflammatory agents are being developed for administration by this route.* Unfortunately, safe and effective substitutes for CFCs in MDIs are not likely to be available in time to meet the requirements of the Montreal Protocol, the international agreement that restricts the production of CFCs.[1]

The goals of this paper are (1) to review the adverse effects of CFCs on the global environment, (2) to describe the role of CFCs in MDI technology, and (3) to place in perspective the risks and benefits of continued use of CFCs in MDIs.

Dr Balmes is Assistant Professor of Medicine, Center for Occupational and Environmental Health, University of California, San Francisco.

A version of this paper was presented by Dr Balmes during the Consensus Conference on Aerosol Delivery, sponsored by the American Association for Respiratory Care, the American Respiratory Care Foundation, and the journal RESPIRATORY CARE, January 10-12, 1991, in Cancun, Mexico.

Reprints: John R Balmes MD, Center for Occupational and Environmental Health, Building 30, 5th Floor, San Francisco General Hospital, San Francisco CA 94110.

*Pharmaceutical Aerosol CFC Coalition. The impact of further CFC restriction on pharmaceutical aerosols and their use in the United States (unpublished report, 1989).

CFCs and the Environment

The chemical stability of CFCs that renders them relatively safe and non-toxic is also what causes them to be so threatening to the global environment. There are no known mechanisms for CFC decomposition in the lower atmosphere (troposphere). Once these compounds are released into the environment, they slowly rise to the upper atmosphere (stratosphere), where they are gradually decomposed by solar ultraviolet radiation. The major CFCs in use today (CFC-11, CFC-12, CFC-113, CFC-114) all have long residence times in the atmosphere, from 60 to almost 200 years.[4] (The numerical identification of CFCs is by a code that indicates how many carbon, hydrogen, chlorine, and fluorine atoms are present.) The first evidence that CFCs were accumulating in the atmosphere came from measurements in the early 1970s.[5,6] Comparison of estimated releases of stable CFCs to the measured atmospheric concentrations showed that very little of the released compounds had decomposed. One positive note is that the rate of accumulation seems to have slowed over the last decade, presumably reflecting the North American ban on the nonessential uses of CFCs in spray cans.[7]

Two major environmental problems associated with CFC accumulation in the atmosphere have been identified: contribution to global warming through the greenhouse effect and depletion of stratospheric ozone. These complex problems will be discussed in brief.

The Greenhouse Effect

Despite the controversy that surrounds the magnitude of the greenhouse effect, it is actually one of the best-established concepts in atmospheric science.[8] Both the extreme heat of the surface of Venus and the frigid surface of Mars can largely be explained by the greenhouse effect. The effect is caused by the presence of gases in the atmosphere that allow sunlight to filter through to warm the surface of the planet but block the escape of radiant infrared energy from the surface back to space. The primary greenhouse gas in Earth's atmosphere is water vapor, but so-called trace gases (such as carbon dioxide, methane, tropospheric ozone, nitrous oxide) and CFCs also contribute to this effect. While the greenhouse gases are relatively transparent to the visible and near-infrared wavelengths that carry most of the energy of sunlight, they also absorb efficiently the larger infrared wavelengths emitted from the earth's surface. Thus, as the concentration of greenhouse gases increases, there is greater warming of the surface by downward reradiation of infrared heat.

What is most controversial about the greenhouse effect is prediction of the degree of warming of the earth's surface that will occur with a given increase in the concentration of trace gases such as CO_2 and CFCs. Several computer models predict climatic conditions that indicate that a doubling of the atmospheric carbon dioxide concentration would lead to global climate warming of about 3-5°C, averaged over the earth's surface.[8,9] Similarly, these climatic models predict that a warming of at least 1°C should have occurred during the past century (over which there was a 20% increase in carbon dioxide concentration). However, this prediction of a 1-degree warming is somewhat larger than what was actually observed, which was approximately 0.5 degree. There are multiple possible explanations for the discrepancy between the prediction and the actual temperature record, but the magnitude of the difference is such that both researchers who believe the current climatic models are valid and those who are skeptical can find support for their respective positions. However, there is no argument that the average temperature for the 1980s made it the warmest decade on record. Whether this recent warming is due to a natural fluctuation or to the increase in trace greenhouse gases is the important unanswered question.

Further research over the next several decades will likely lead to a definitive answer concerning the validity of the current estimates of the climatic impact of the buildup in greenhouse gases. The debate is over whether we can afford to wait until definitive data have been collected. Five degrees C is the difference between the global average surface temperature during the Ice Age 18,000 years ago and the present temperature. If the current climatic models are valid, then we may experience a rise of similar magnitude over the next century. The consequence of such a rapid increase in temperature

cannot be precisely projected, but it is possible that the sea level would rise 0.5-1.5 meters, that the flow of rivers in the American Southwest would be reduced by 20%, and that the corn belt in the Great Plains would 'move' north and east into Canada.[8]

In order to discuss appropriate policy responses to the threat of global warming due to the greenhouse effect, one must consider the contributions of the various trace gases. The contribution of carbon dioxide currently dominates because of the magnitude of emissions and long residence time in the atmosphere; it has been estimated that carbon dioxide was responsible for approximately 80% of the global warming potential generated in 1985.[10] On a weight basis, the global warming potential of CFCs is much greater than that of carbon dioxide (Table 1). One prediction indicates that the total contribution of other trace gases to global warming is more likely than not to exceed the contribution from carbon dioxide by the year 2050.

Table 1. Relative Warming Potential of Some Trace Atmospheric Gases*

Gas	Atmospheric Residence Time (years)	Global Warming Potential
CO_2	230	1
N_2O	160	180
HCFC-22	15	410
CFC-11	60	1,300
CFC-12	120	3,700

*Adapted, with permission, from Reference 10.

What are high-yield strategies for reducing emissions of greenhouse gases and slowing the rate of global warming? Given the uncertainty about the actual rate of temperature increase, which will not be resolved for some years, it has been suggested that the best policy actions to take at the present time are those that are otherwise beneficial to society, such as investing in more efficient use and production of energy.[8,9] Reductions in emissions from the burning of fossil fuels would reduce acid rain and dependence on foreign oil as well as slowing greenhouse gas accumulation.

Chlorofluorocarbon emissions are already being reduced by international agreement because of their negative effect on stratospheric ozone, and this action should have a positive impact on the greenhouse effect. However, the need for compliance must be emphasized, as it has been predicted that even if 1985 emission rates of CFC-11 and CFC-12 were to remain constant, the concentrations of these compounds would more than double within the next 40 years because of their long atmospheric residency times.[11]

Depletion of Stratospheric Ozone

The portion of the atmosphere between 10 and 50 km above the earth's surface is known as the stratosphere. Ozone (O_3) is formed at high altitude (> 20 km) in photolytic reactions as follows:

$$h\nu + O_2 \rightarrow O + O, \text{ and}$$
$$O + O_2 + M \rightarrow O_3 + M,$$

where M is any third body capable of absorbing the energy of the reaction,[12] and hν indicates light energy.

Ozone absorbs the light energy of ultraviolet (UV) photons < 315 nm in the following reaction:

$$O_3 + h\nu \rightarrow O + O_2.$$

This reaction is responsible for preventing virtually all UV radiation in the C-wavelength range (240-290 nm) and much of the UV radiation in the B-wavelength range (290-320 nm) from reaching the earth's surface. It has been estimated that a 10% reduction in stratospheric ozone would allow increases in UV radiation of 20% at 305 nm, 250% at 290 nm, and 500% at 287 nm.[13]

Ozone chemistry in the stratosphere is quite complex, and there are multiple chemical pathways by which ozone can be destroyed.[12] However, the presence of active free radicals will catalyze the conversion of ozone to oxygen by the following reactions:

$$X + O_3 \rightarrow XO + O_2, \text{ and}$$
$$XO + O \rightarrow X + O_2,$$

where X is chlorine, bromine, nitric oxide (NO), hydrogen, hydroxyl, or hydrogen superoxide radical.

The net result is $O + O_3 \rightarrow 2O_2$, so that the active radical is free to catalyze further conversion of

ozone to oxygen. Gribben has suggested that a single chlorine radical may destroy up to 100,000 molecules of ozone.[14]

The major sources of stratospheric chlorine are CFCs, carbon tetrachloride, and methylchloroform.[12] The major sources of stratospheric bromine are halons, especially those used in modern fire extinguishers. Important sources of stratospheric nitrogen radicals are microbial production of nitrous oxide in soil and the combustion of fossil fuel, especially by high-flying, supersonic aircraft. The atmospheric concentration of all of these compounds is increasing as a result of human activity. Unfortunately, the atmospheric retention times of these compounds tend to be extremely long.

Molina and Rowland first hypothesized in a 1974 paper that photolytic decomposition of CFCs in the stratosphere would generate chlorine radicals that would in turn cause the catalytic destruction of ozone.[6] However, worldwide public attention became focused on the problem of ozone depletion only after the report by Farman et al of an Antarctic "ozone hole" in 1985.[15] The total atmospheric concentration (or column density) of ozone is measured in Dobson units, and Farman's group indicated that the column density measured at a station in Antarctica in October fell from about 320 Dobson units in 1975 to about 200 Dobson units in 1984. Their initial findings have been confirmed by other ground measurements, and satellite monitoring has demonstrated that the area covered by the ozone hole currently covers most of the continent. In three of the last four years, the column density of ozone has fallen to below 125 Dobson units, so that the scope of the problem appears to be rapidly increasing.[16]

Although the problem of stratospheric ozone depletion is greatest at high latitudes (apparently due to high seasonal concentrations of chlorine radicals as a result of reactions on the surface of particles in polar stratospheric clouds), recent evidence suggests that the problem affects the entire globe. An analysis of data from a network of ground-based stations by the U.S. National Aeronautics and Space Administration indicates that there have been annual reductions in the column density of ozone in the range of 1.7-3.0% over the mid-latitudes of the northern hemisphere.[12]

In retrospect, loss of ozone over Antarctica was evident in the mid-1970s, when the concentration of chlorine in the stratosphere was approximately 2.5 parts per billion.[12] The current concentration is much higher, and projections for continued growth suggest that a return to the level of the mid-1970s, even over a century, requires an immediate dramatic reduction in CFC emissions.

What are the biological consequences of global ozone depletion? When the ozone hole appears in the Antarctic spring, increased UV-B radiation reaches the surface of the continent and, perhaps more importantly, the surrounding ocean. It has been demonstrated that UV-B radiation can penetrate up to 20 meters of ocean depth.[17] Much research is being conducted on the effects of the increased UV radiation on the Antarctic Ocean ecosystem. Some investigators fear that the increased dose of UV radiation each spring will harm phytoplankton, the microscopic free-floating algae that form the basis of the marine food chain. If phytoplankton are affected, then so will be krill, the tiny invertebrates that feed on them and, in turn, fish, sea birds, and marine mammals. The data reported to date do not allow firm conclusions to be drawn about the extent of damage to the Antarctic ecosystem.

It is the potential for damage to DNA from stratospheric ozone depletion that is of the greatest concern. Ultraviolet light in the B and C wavelengths spans the full photoabsorption spectrum of DNA. Because the stratospheric ozone layer shields the earth's surface from virtually all UV-C and most of the less damaging UV-B, the ozone layer's integrity is vital to the protection of the genome of the vast majority of living organisms. With regard to human health, UV exposure is most strongly linked to the etiology of cataracts and skin cancer. Chronic UV exposure appears to be the major determinant of basal-cell and squamous-cell carcinomas of the skin in Caucasian populations, and there is a negative correlation with latitude.[18] While the relationship between UV exposure and malignant melanoma appears to be somewhat more complex, multiple epidemiologic studies have established that there is a clear negative correlation between melanoma incidence and latitude.[13]

Melanoma incidence and mortality are rising in Caucasian populations around the world. In Australia, melanoma death rates have increased fivefold over the past 50 years.[19] The U.S. Environmental Protection Agency has estimated that a 1% decrease in stratospheric ozone concentration will result in a 1-3% increase in non-melanoma skin cancer and a 0.8-1.5% increase in deaths due to malignant melanoma.[13] One model of ozone depletion predicts a 6% reduction in global ozone in the year 2030 compared to 1970.[13] The prognosis may be much more serious than this model indicates because the average annual decrease for regions below 60 degrees S latitude is already greater than 6%.[20]

Because of the enormity of the potential impact of stratospheric ozone depletion on human health, 27 nations signed the Montreal Protocol in September 1987 to cut CFC production by 50% by 1999.[1] The protocol called for a continued review of the applicable science, and it has become clear from data collected after the Montreal meeting that more drastic action is required. Only an immediate 85% reduction in CFC emissions was predicted to stabilize atmospheric concentrations at their current levels. At the most recent meeting of the Parties to the Montreal Protocol in London in June 1990, it was agreed to entirely eliminate CFC production by the year 2000.

The rapid phaseout of CFC production will apply considerable economic pressure to pharmaceutical manufacturers of MDIs. It will be increasingly costly and difficult for these manufacturers to obtain sufficient supplies of the various CFCs upon which the proper functioning of current devices depends.

Metered Dose Inhalers

Pressurized MDIs consist of four major components: (1) the pharmaceutical formulation, (2) a pressurizable container, (3) a metering device designed to control the dispensing of precise doses of the formulation, and (4) a mouthpiece adapter that allows activation of the discharge mechanism of the aerosol, contains the small orifice from which the aerosol is discharged, and provides a conduit to the patient's mouth. The majority of MDI products use suspension formulations due to the solubility properties of most of the active drugs and the limited solvent properties of the commonly used propellants. Sometimes solution systems employing a co-solvent such as ethanol can be developed, but there is a preference for suspension systems because of enhanced chemical stability, better control over particle size, and less respiratory-tract irritation.

The typical ingredients of MDI-suspension formulations are the active drug, a suspending agent, and a mixture of CFCs that serve as the suspending medium and as the propellant. All MDI products currently use CFC-12 as the primary propellant, while either or both of two other CFCs with lower vapor pressures, CFC-11 and CFC-114, are added to moderate the pressure and volatility of the final product. A small amount of a suspending agent with surface-active properties, such as sorbitan trioleate, oleic acid, oleyl alcohol, or soya lecithin, is almost invariably included. While the drug must be insoluble, the suspending agent must remain fully soluble in the propellant blend. Chlorofluorocarbon-11 is the agent commonly used to provide the required solvent properties for the propellant blend.

The unique properties of the liquefied CFC gases provide the basis of function for all current pressurized MDIs. In order for an inhaled medication to be effective, a significant fraction of the administered drug must be delivered to the patient's mouth in a respirable particle size. Pressure alone (generally between 40 and 60 psi) is not sufficient to generate an aerosol of respirable particle size. The liquefied CFC gases used in current MDIs will remain liquid at ambient temperatures if they are held in sufficiently strong containers. However, if a liquefied CFC gas is released at a temperature above its boiling point, it explosively flash-boils and creates a fine aerosol of whatever was suspended or dissolved in it.

The liquefied gases that can be used in MDIs must have appropriate physical and chemical characteristics. These gases must be non-toxic and safe (eg, nonflammable). They must have vapor pressures and boiling points such that an appropriate pressure is generated at ambient temperatures. The liquefied propellant mixture must have a density

similar to that of the drug being delivered (so that the drug does not settle rapidly after the vial is shaken prior to use) and appropriate solvent characteristics as discussed above. The three common CFC refrigerant gases that are currently used in MDIs meet all of these requirements (Table 2).

Table 2. Properties of CFC Gases Commonly Used in MDIs

Gas	Boiling Point (°C)	Vapor Pressure (psig, 20°C)	Density (g/mL, 20°C)
CFC-11 ($CFCl_3$)	24	-1.8	1.49
CFC-12 (CF_2Cl_2)	-30	67.6	1.33
CFC-114 (CF_2ClCF_2Cl)	4	11.9	1.47

As previously mentioned, CFC-12 is used in all MDIs, and provides most of the energy used to generate the requisite fine aerosol. Chlorofluorocarbon-114 is used in many MDIs to moderate pressure, alter density, and provide desired solvent characteristics. Chlorofluorocarbon-11 is not actually a propellant, because it has a boiling point near room temperature and can be handled in liquid form at atmospheric pressure if slightly cooled; its primary role is that of solvent for the suspending agent(s). Because of its lack of volatility, CFC-11 plays an important role in the MDI manufacturing process. A 'concentrate' of the active drug and suspending agent in CFC-11 is produced initially; the balance of propellant in the formula is then either supplied to the MDI separately by injection through the metering valve or combined with the concentrate and supplied to the MDI as a refrigerated blend.

Worldwide CFC Production and Use in MDIs

In 1988, the total world consumption of CFCs was over 1,000,000 tons.[21] The quantity of CFC gases currently used worldwide in MDIs is approximately 4,500 tons, or from 0.4-0.5% of annual CFC production.[22] While any CFC emissions will have negative effects on environmental quality, the contribution from this level of consumption to the overall problem is small. However, manufacturers of CFCs will be cutting production of ozone-depleting CFCs drastically over the next few years such that it will become progressively more difficult for the pharmaceutical industry to purchase these compounds. The manufacturers of MDIs are even considering purchasing one or more of the CFC production facilities that will be closed as the chemical industry converts to large-scale, commercial production of hydrofluorocarbon (HFC) and hydrochlorofluorocarbon (HCFC) refrigerants, because the latter cannot be produced at existing plants. Recycling is being done by one major CFC manufacturer, but because of potential contamination of recycled CFCs with toxic chemicals (eg, polychlorinated biphenyls and dioxins) as well as with lubricant oils, this option is not available to the pharmaceutical industry.

Alternatives to CFCs in MDIs

The two classes of compounds that are being commercially developed as replacements for CFCs are HFCs and HCFCs. The ozone-depletion potential (ODP) of various compounds can be calculated by dividing the cumulative ozone depletion caused by release of that compound by the equal emission (by weight) of a reference ozone depleter such as CFC-11 (Table 3).[21] The HFCs do not contain chlorine and therefore have an ODP of zero. The absence of chlorine, however, tends to cause HFCs to have higher vapor pressures and lower solubility than CFCs. While the HCFCs contain chlorine, the addition of hydrogen atoms allows them to decompose in the troposphere, so that very little of the chlorine reaches the stratosphere. Thus, the ODP of HCFCs, as a class, is significantly less than that of CFCs.

The compound that the pharmaceutical industry currently favors as a replacement propellant for

Table 3. Relative Ozone-Depleting Potential of Some CFC and HCFC Gases*

Gas	Ozone-Depleting Potential
CFC-11	1.0
CFC-12	1.0
CFC-114	0.7
HCFC-141b	0.1
HCFC-142b	0.05
HCFC-123	0.003
HCFC-124	0.002
HFC-134a	0

*Adapted, with permission from, Reference 21.

MDI use is HFC-134a, because it has a vapor pressure similar to that of CFC-12. However, there will still be a need for a second, less-volatile gas to moderate the high pressure of HFC-134a, and many of the suspending agents in current use are not very soluble in this compound.

A major concern of the pharmaceutical industry is to find a suitable replacement for CFC-11, which serves as the low-pressure co-solvent in most MDI formulations.* The candidates include ethanol, HCFCs, and hydrocarbons (eg, *n*-butane, *n*-pentane, and isopentane). There are problems with each of these candidates. Most drugs have only a limited solubility in ethanol such that neither stable solution nor stable suspension systems can easily be formed. Although several HCFC gases (123, 124, 141b, and 142b) have boiling points in the range that makes them appropriate candidates for replacement of CFC-11, MDI manufacturers are somewhat reluctant to gear up for HCFC use out of fear that these compounds may eventually be restricted because they do have some potential to deplete ozone. Another significant problem with HCFC use in MDIs is flammability. The most attractive HCFC replacement for CFC-11 in terms of chemical properties and flammability is HCFC-123. Unfortunately, this compound appears to be somewhat toxic in initial testing undertaken by producing companies. Finally, several non-ozone-depleting hydrocarbons are possible candidates based on their boiling points and solvent properties, but remain unattractive due to flammability and potential toxicity.

The reformulation of MDI products with replacement propellants for the current CFC mixture will take considerable time and resources. First, chemical manufacturers must produce sufficient quantities of potential CFC replacements to allow pharmaceutical industry testing. Next, compatibility with current MDI manufacturing processes, container vials, and metering valves must be assessed. Chronic inhalational toxicologic testing of the replacement propellants would then likely take several years. Once new formulations including the replacement propellants have been developed, these also will be subject to chronic inhalational toxicologic testing. If a new formulation appears to be safe and non-toxic at this point, application can then be made to the Food and Drug Administration for permission to conduct stability and clinical efficacy testing. A coalition of pharmaceutical aerosol manufacturers has estimated that if all goes well with each of the above-outlined steps (an unlikely scenario), a minimum of 8 years would be required to develop and adequately test reformulated MDI products.*

*Pharmaceutical Aerosol CFC Coalition. The impact of further CFC restriction on pharmaceutical aerosols and their use in the United States (unpublished report, 1989).

Conclusions

Both the number of persons with asthma and the number of deaths attributable to asthma have been increasing in the U.S. over the past decade. The number of persons with chronic obstructive pulmonary disease (COPD) has also been increasing, although not as dramatically, probably as a result of decreased cigarette smoking. Approximately 25 million Americans suffer from these conditions,[23] and a large proportion of these people rely on MDI products for relief of respiratory symptoms and prophylaxis against acute exacerbations. While alternatives to the use of MDIs do exist, it is unlikely that all patients with asthma and COPD will be able to effectively and conveniently use the available substitutes. Nebulized aqueous solutions of bronchodilators and corticosteroids are effective but require equipment that is not easily portable and takes more time to deliver an effective dose than MDIs. Dry powder inhalers (DPIs), which use the energy of the patient's inspiratory effort to disperse the drug powder, have been available for some medications for a number of years (eg, the Spinhaler for sodium cromoglycate from Fisons and the Rotahaler for albuterol or beclomethasone from Allen and Hanburys). While the fact that these inhalers are breath-activated allows some patients to achieve better dosing, it is equally true that patients in respiratory distress may not have adequate inspiratory flowrate to properly activate DPIs. A further problem with older models of DPI is that they require the loading of a gelatin capsule containing the drug powder prior to each use. Multidose DPIs have been recently introduced (eg, Diskhaler from Allen and Hanburys and Turbuhaler from Astra) that are more convenient.[22] It appears likely that a significant proportion of patients can be successfully switched from MDIs to DPIs, but continued

MDI use will be desirable for many. A recent United Nations Environment Programme technical report estimated that DPIs were not suitable for at least 10% of patients (small children, the elderly, and persons with persistent airway hyperresponsiveness).[1]

In summary, the commercial use of CFC gases is being phased out by international agreement because these gases have been linked to the depletion of stratospheric ozone. It has also been established that CFCs are greenhouse gases that contribute to global warming. Pressurized MDIs are currently an important component of the modern therapeutic approach to the treatment of asthma and COPD for which a continued need is likely to exist for the forseeable future. Unfortunately, CFCs are required for the proper function of all conventional MDIs. Because it will take a number of years to develop and test replacement propellants as well as the reformulated MDI products, national and international governmental agencies will need to design specific policy responses for the problem of CFC use in MDIs. The Parties to the Montreal Protocol on Substances that Deplete the Ozone Layer appear to recognize this need because they have requested that an assessment of "the toxicology, flammability, energy efficiency implications, and other environmental and safety considerations of chemical substitutes, along with an analysis of the likely availability of substitutes for medical uses" be performed by mid-1992 (personal communication, Terrance Coyne MD, St Paul MN, Chairman, Pharmaceutical Aerosol CFC Coalition, November 1990).

REFERENCES

1. Technology Review Panel/Technical Options Committee on Aerosols, Sterilants and Miscellaneous Uses. Aerosols, sterilants and miscellaneous uses of CFCs (pursuant to the Montreal Protocol). Nairobi, Kenya: United Nations Environment Programme, 1989.
2. Bone RC. Step care for asthma (editorial). JAMA 1988;260:543.
3. British Thoracic Society, Research Unit of the Royal College of Physicians of London, King's Fund Centre, National Asthma Campaign. Guidelines for management of asthma in adults: 1—chronic persistent asthma. Br Med J 1990;301:651-653.
4. Fisher DA, Hales CH, Wang W-C, Ko MKW, Sze ND. Model calculations of the relative effects of CFCs and their replacements on global warming. Nature 1990; 344:513-516.
5. Lovelock JE. Atmospheric fluorine compounds as indicators of air movements (letter). Nature 1971;230: 379.
6. Molina MJ, Rowland FS. Stratospheric risk for chlorofluoromethanes: chlorine atom-catalysed destruction of ozone. Nature 1974;249:810-812.
7. Rasmussen Khalil MAK. Atmospheric trace gases: trends and distributions over the last decade. Science 1986;232:1623-1624.
8. Schneider SH. The greenhouse effect: science and policy. Science 1989;243:771-781.
9. White RM. The great climate debate. Sci Am 1990; 263:36-43.
10. Lashof DA, Ahuja DR. Relative contributions of greenhouse gas emissions to global warming. Nature 1990; 344:529-531.
11. Dickinson RE, Cicerone RJ. Future global warming from atmospheric trace gases. Nature 1986;319:109-115.
12. McElroy MB, Salavitch RJ. Changing composition of the global stratosphere. Science 1989;243:763-770.
13. Jones RR. Ozone depletion and cancer risk. Lancet 1987;2:443-445.
14. Gribben J. The hole in the sky: man's threat to the ozone layer. London: Corgi Books, 1987.
15. Farman JC, Gardiner BG, Shanklin JD. Large losses of total ozone in Antarctica reveal seasonal ClO_x/NO_x interaction. Nature 1985;315:207-210.
16. Kerr RA. Another deep Antarctic ozone hole (news report). Science 1990;250:370.
17. Roberts L. Does the ozone hole threaten Antarctic life (news report). Science 1989;244:288-289.
18. Urbach F, Epstein JH, Forbes PD. Ultraviolet carcinogenesis: experimental global and genetic aspects. In: Fitzpatrick TB, et al, eds. Sunlight and man: normal and abnormal photobiological responses. Tokyo: University of Tokyo Press, 1974:259-283.
19. Holman C, Mulroney C, Armstrong B. Epidemiology of preinvasive and invasive malignant melanoma in Western Australia. Int J Cancer 1980;25:317-323.
20. Stolarski R, Krueger A, Schoebel M, McPeters R, Newman P, Alpert J. Nimbus 7 satellite measurements of the springtime Antarctic ozone depletion. Nature 1986; 322:808-811.
21. Manzer LE. The CFC-ozone issue: progress on the development of alternatives to CFCs. Science 1990;249: 31-35.
22. Newman SP. Metered dose pressurized aerosols and the ozone layer (editorial). Eur Respir J 1990;3:495-497.
23. 1989 National Health Interview Survey. Hyattsville MD: National Center for Health Statistics, Centers for Disease Control, 1990.

Topical Dosage For Young Asthmatic Children With M.D.I. Aerosol Medications

Young children with asthma can now obtain the benefits of aerosol medication manufactured by M.D.I.'s with the new AEROCHAMBER® WITH MASK from Monaghan Medical Corporation. This innovative device permits the use of all aerosol medications manufactured by M.D.I currently available for treatment of acute wheezing.

Movement of a diaphragm in the mask is a helpful indication that the mask is properly sealed to the child's face. Proven efficacy with metered dose inhalers, combined with the convenience of the AEROCHAMBER WITH MASK, allows you to give aerosolized medications to young children practically any time or any place, effectively and conveniently. The AEROCHAMBER WITH MASK is very inexpensive when compared to the use of a compressor with S.V.N. and mask. The AEROCHAMBER WITH MASK is easy to use, easy to clean, compact enough to fit in a mother's purse, and best of all, delivers the results you expect when treating asthma and bronchiolitis.

Note: "Metered dose inhalers and Aerochamber with Mask are to be used by a responsible adult under the direction of a physician."

Improving The Future Today

MONAGHAN MEDICAL CORPORATION

P.O. Box 2805, Plattsburgh, NY 12901 800/833-9653 In NY 518/561-7330 Fax 518/561-5660

1. Broochodilators Effect of Fenoterol and Ipratropium Bromide in Iofaots With Acute Wheezing: Use Of MDI With A Spacer Device. Mallol, J., Barrueto, L. Girardi, G. aod Toro, O. Pediatric Pulmonology 3:352-356 (198")

Circle 106 on reader service card

Calendar of Events

Not-for-profit organizations are offered a free advertisement of up to eight lines to appear, on a space-available basis, in Calendar of Events in RESPIRATORY CARE. Ads for other meetings are priced at $5.50 per line and require an insertion order. Deadline is the 20th of month two months preceding the month you wish the ad to run. Submit copy and insertion orders to: Calendar of Events, RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229-4593.

AARC & AFFILIATES

September 18-20 in Myrtle Beach, South Carolina. The SCSRC hosts its Annual State Meeting at the Landmark Hotel. Contact Sandra Cassell at (803) 765-7201.

September 19-20 in Sebasco, Maine. The MSRC presents its Annual Fall Conference, "The Maine Event," at Sebasco Lodge. Topics include case studies of difficult ventilation, hyperbaric medicine, ventilation equipment in the home, and CLIA regulations. Contact Jane Barthelette for additional information at (207) 596-8488.

September 19-20 in Indianapolis, Indiana. The ISRC presents its 18th Annual Fall Seminar at the Holiday Inn-North. The two full days feature lectures, specialty sections, exhibits, and Sputum Bowl competition. Topics include the future of ventilation, home care accreditation, pediatric rehabilitation, MDI therapy, total quality management, asthma, critical care, and Exosurf use. Contact Kathleen Lee, Ivy Tech, PO Box 1763, Indianapolis IN 46206. (317) 921-4402.

September 25-27 in Minneapolis, Minnesota. The MSRC presents its 22nd Annual Education Conference at the Holiday Inn West. Activities begin with the 3rd annual "Duffers Open" golf tournament and the MSRC "Quiz Bowl." Dr Ronald Cranford, nationally known biomedical ethicist, gives the keynote lecture. Contact Michele Patnaude at (612) 347-2546.

September 26-27 in Napa, California. The CSRC Chapter 10, the American Lung Association of the Redwood Empire, and the Respiratory Therapy Program at Napa Valley College present the 9th Annual Napa Valley Conference "Current Concepts in Cardiopulmonary Care." Topics include home care, surfactant replacement therapy, transesophageal echocardiography, AIDS treatments, hyperbaric medicine, and issues in bronchodilator therapy. Also, Patrick Dunne MEd RRT, AARC president, presents "Respiratory Care in the 21st Century." Nine CEUs. Contact Kate Benscoter at (707) 253-3141.

September 26-27 in Hays, Kansas. The KSRC invites all RCPs to the 5th Annual Western Kansas Seminar. Topics include "RC in Canada," "Caregiver's Role in Maintaining Organ Donor Candidates," "Respiratory Care of the Burn Victim," "The Lung Cancer Patient," and "Stabilization/Transportation of the Acute Trauma Victim." Contact Don Hedden RRT, Hays Medical Center-Hadley Campus, 201 E 7th, Hays KS 67601. (913) 628-9310.

September 29-October 1 in Coeur d'Alene, Idaho. The ISRC presents its Annual Convention at The Coeur d'Alene Resort. Speakers include James Stoller MD, John Luce MD, and Forrest Bird PhD. The convention features lectures, exhibits, Sputum Bowl competition, and a dance/boat cruise on beautiful Lake Coeur d'Alene. For information, contact Becky Reagan RRT or Alan Terry RRT, Respiratory Care Department, Kootenai Medical Center, 2003 Lincoln Way, Coeur d'Alene ID 83814. (208) 664-7430.

October 2-4 in Gaylord, Michigan. The MSRC presents its Annual Fall Conference at the Sylvan Treetops Resort. Program topics include trauma, critical care, aerosol therapy/pharmacology update, pediatrics, management, and ethics. The Pulmonary Rehabilitation Membership Section offers presentations on the metabolic cart and nutrition. Special events include a golf outing on an 18-hole championship course, wine and cheese reception, outdoor steak fry, and volleyball. Contact Beth Hill RRT, Bay Medical Center, Respiratory Care Department, 1900 Columbus Ave, Bay City MI 48708. (517) 894-3166.

October 6-9 in Cancun, Mexico. The LSRC celebrates Respiratory Care Week by sponsoring the Cancun Breeze Management Seminar at Conrad Resorts International in Cancun. For more information and/or a registration form, contact Jim Lanoha at (504) 387-7080.

October 8-9 in Honolulu, Hawaii. The HSRC presents the 18th Annual Respiratory Care Conference at the Hilton Hawaiian Village Hotel. Keynote speaker is AARC President Patrick Dunne MEd RRT. Contact Helen Ono, 1717 Palolo Ave, Honolulu HI 96816. (808) 547-9532.

October 12 in Long Beach, California. The CSRC Chapter IV and the American Lung Association of Long Beach present Respiratory Care Workshop XVII at the Clarion Hotel. Contact Nan Evans, American Lung Association of Long Beach, 1002 Pacific Ave, Long Beach CA 90813-3098. (213) 436-9873.

October 15-17 in Atlantic City, New Jersey. The NJSRC presents the 1991 Shore Conference at Trump Castle by the Bay. Contact Gail Horn RRT, Kennedy Memorial Hospital-Cherry Hill, PO Box 5009, Cherry Hill NJ 08034. (609) 488-6847.

October 18 in Long Island, New York. The Southeastern Chapter of the NYSSRC presents its 23rd Annual Symposium, "Professional Practice Update 1991." The conference will be held at the Marriott Hotel in Uniondale. Speakers include Patrick Dunne MEd RRT (Continuous Quality Improvement); Marty Douglass MA (Clinical Applications of Noninvasive Ventilation); Barbara Finger JD (Clinical Incident Documentation); Thomas East PhD (The Use of Computers in Respiratory Care); Aimee Telsey MD (Artificial Surfactant Replacement); and Fred Mindermann BS RRT (Dynamic Interaction Ventilation). Contact Ken Axton RRT at (516) 444-3180.

October 25 in Bear Mountain, New York. The Hudson Valley Chapter of the NYSSRC presents its annual educational seminar at the Bear Mountain Inn. The theme for the 1-day event is "Pediatric Ventilator & Respiratory Care." The magnificent landscape, a buffet lunch, the scenic Hudson River, and fall foliage complement the event. Contact Mike Aiello RRT, Box 150, Glenham NY 12527, (914) 795-5340.

October 30-31 in Sturbridge, Massachusetts. The MSRC presents its 14th Annual Meeting at the Sheraton Sturbridge Resort and Conference Center. Topics include bronchoscopy, home care, asthma diagnosis and therapy, ECMO, and sleep studies. Special feature is a debate covering the pros and cons of pentamidine and ribavirin. Contact Gina Farquharson RRT, 16 Bartlett St, Pembroke MA 02359, (617) 293-6090.

OTHER MEETINGS

September 14-October 27—CRTT Exam Review Workshops. Respiratory Review Workshops (RRW) will be conducting entry-level certification examination reviews to prepare individuals taking the November CRTT exam. The workshop is taught by Gary Persing BS RRT, director of clinical education in the respiratory therapy program at Tulsa Junior College. This highly successful 2-day workshop will be held in San Antonio TX on Sept 14-15; Minneapolis MN on Sept 21-22; Tulsa OK on Sept 28-29; Dallas TX on Oct 12-13; and Shreveport LA on Oct 26-27. The AARC has approved this workshop for 16 CRCE credits. Contact RRW at (918) 455-0503.

September 20 in Beaumont, Texas. The Respiratory Care Services Department of St Elizabeth Hospital hosts its 3rd Annual Educational Seminar at the Beaumont Plaza Holiday Inn. Lectures and hands-on workshops cover a wide variety of topics of interest to respiratory and nursing professionals. Contact Greg Rodgers RRT at (409) 899-7065.

September 27 in Philadelphia, Pennsylvania. Main Line Health Inc presents "Current Perspectives in Adult and Neonatal Pulmonary Care" at the Society Hill Sheraton Hotel. Fee: $100 physicians; $75 RTs, RNs, and PAs (includes breakfast and lunch). Hotel and tour packages available. Contact Bob Kay or Bill Howell, Bryn Mawr Hospital, 130 S Bryn Mawr Ave, Bryn Mawr PA 19010, (215) 526-3340.

September 27 in Oxnard, California. The American Lung Association of Ventura County presents "Pandora's Box of Pulmonary Medicine." This year's guest speaker, Thomas Petty MD, discusses pulmonary rehabilitation. Contact Barbara Weinberg, American Lung Association, (805) 988-6023.

October 7 in Rochester, Minnesota. The Mayo Department of Anesthesiology/Respiratory Therapy Program presents the 1st Annual Paul Didier Distinguished Lecture. Dr Irwin Ziment will present "Our 5,000-Year Attack of Asthma." Contact Penny Marshall, Charlton 2, Mayo Clinic, Rochester MN 55905, (507) 284-9694.

A World Of Opportunity For Traveling Professionals.

At StarMed, we provide the professional opportunities and personal satisfaction you want as a traveling **RRT, CRTT** or **CRNA.** • Choice of 13-week assignments from the country's finest hospitals. • The Golden Wings benefits program – the most comprehensive pay, bonus and insurance package in the industry. • Paid travel and housing expenses. • Career counseling and support from your personal recruiter.

If you're a qualified professional with at least one year's experience, and you're looking for temporary or permanent placement, call StarMed. It'll do you a world of good.

STAR·MED
STAFFING CORPORATION

Toll-free 1-800-STARMED (782-7633)

Circle 127 on reader service card

AEROSOL TREATMENT AND SPUTUM CHAMBER

J.H. Emerson Co.
22 Cottage Avenue • Cambridge, MA 02140

For the safe delivery of aerosolized drugs (Pentamidine) and for sputum induction procedures, the **Emerson Model 7-AT Chamber** provides a convenient alternative to complete ventilation system installations.

FEATURES:

- Self-contained
- High Air Exchange Rate
- Alarms
- Sturdy Construction
- Convenient Size
- Requires No Costly Disposables

(617) 864-1414
(800) 252-1414

Circle 120 on reader service card

October 11-13 in Clearwater Beach, Florida. The American Lung Association of Florida hosts the conference "Respiratory Care for the Pediatric and Neonatal Patient." Contact Richard T Doggett, American Lung Association of Florida, PO Box 8127, Jacksonville FL 32239. (904) 743-2933.

October 11-13 in Marina del Rey, California. Children's Hospital of Los Angeles, Saddleback Memorial Medical Center, and SensorMedics Corp host the Infant and Pediatric Pulmonary Function Testing Conference. For a brochure and more information, call (800) 231-2466, ext 700.

October 17-18 in Birmingham, Alabama. The Children's Hospital of Alabama presents its 1st Annual Perinatal-Pediatric Respiratory Care Clini-Course at the Radisson Hotel. Topics include assisted ventilation of the neonate, high-frequency ventilation, pressure support ventilation, mechanical ventilation of the asthmatic patient, pediatric trauma, mask ventilation, delivery of aerosolized drugs, and continuous aerosolization. Speakers include Waldemar Carlo, Robert Kacmarek, Allen Goldberg, and Joseph Rau. Contact Susan Forrest at (205) 939-9675.

October 18 in Cincinnati, Ohio. The University of Cincinnati presents a 1-day course entitled "Understanding Lung Function Tests." Contact Occupational Pulmonary Services at (513) 558-1234.

December 6 in Cincinnati, Ohio. The University of Cincinnati presents a 1-day course entitled "Spirometry Refresher—Update." This course reviews recent changes in spirometry testing standards, guidelines, and interpretation techniques. Contact Occupational Pulmonary Services at (513) 558-1234.

January 20-27 in Bahamas Cruise/Orlando Tour. Dream Cruises' "Stress Busters Cruise" for continuing education combines lectures and workshops throughout the week. $795 (per person/double occupancy) inside cabin or $825 (per person/double occupancy) outside cabin. Price includes airfare, cabin, hotel, car, transfers, with food and entertainment provided aboard ship. Contact Kathy Kearney at (800) 462-3628, or write 10882 LaDona Ave, Garden Grove CA 92640.

February 12-14 in Mexico City, Mexico. The Consejo Mexicano de Inhaloterapia presents the 1st International Congress of Respiratory Therapy at the Hotel Paraiso Radisson Perisur. International speakers and exhibits featured. For more information, contact Dr Hector León Garza at 011-525-588-7386, or fax 011-525-578-8952.

No Regrets... With Ambu® Res-Cue Key.

Effective Contact Prevention for CPR.

When saving a life must be your only concern, Ambu has developed a mask made of non-toxic transparent plastic and fitted with a one-way valve that prevents the transmission of infection during emergency ventilation.

What's more, Res-Cue Key is contained in a small, easily opened key ring so it can always be carried with you . . . always ready to use.

Life and no regrets.

For use by CPR-trained personnel only.

Ambu®

7476 New Ridge Road
Hanover, Maryland 21076

Telephone: 1-800-AMBU INC
Telefax: 1-301-850-4699

AMB-101-A 06/90 AARC Times

Circle 114 on reader service card

DeVilbiss Aerosol Management: From Infancy to Adolescence.

The DeVilbiss complete line of aerosol management products assists you in prescribing a total respiratory therapy program for your patients. Convenient and effective, these products help insure compliance for patients who require at-home aerosol therapy and monitoring.

Pulmo-Aide®

The principal compressor/nebulizer for more than 25 years, Pulmo-Aide provides optimum utilization of medication in the home or health care environment. Pulmo-Aide operates with either aerosol mask or mouthpiece and comes with a *five-year warranty.*

Pulmo-Aide® Traveler™

Ideal for the adolescent patient with an active lifestyle, Pulmo-Aide Traveler is designed for portability (AC, DC and battery) with the same high-output efficiency of Pulmo-Aide. Because it can be used in any environment, Pulmo-Aide Traveler is an important element in patient compliance.

Pulmo-Graph™

DeVilbiss' peak flow monitor is a significant part of a total therapy program. A study by the *National Heart, Lung, and Blood Institute* stressed the importance of using a peak flow monitor for home monitoring of patients with asthma.

Founded by a doctor in 1888, DeVilbiss today is a leader in aerosol therapy products worldwide. So, when prescribing aerosol therapy for your patients, insist on the dependability of DeVilbiss.

Circle 119 on reader service card

Send today for your *free* supply of our pamphlet, **Parents Guide to Asthma.** Informative and easy-to-understand, it answers the most commonly asked questions about asthma. You'll find it a valuable addition to your patient education program.

Doctor_____

Facility_____

Address_____

City_____

State_____ Zip_____

Phone_____

Quantity_____

Mail to DeVILBISS,
P.O. BOX 635, DEPT. 1200
SOMERSET, PA 15501-0635.

DEVILBISS

HEALTH CARE WORLDWIDE

We add life to every breath.™

814-443-4881 • 800-DeV-1988
Somerset, PA 15501-0635 U.S.A.

CANADA • FRANCE • GERMANY • JAPAN • U KINGDOM

© 1991 DeVilbiss Health Care, Inc.

Pulmonary Physiology Supervisor

Acting as the Technical Director for this Academic state-of-the-art Laboratory, you'll supervise and perform pulmonary function testing, develop related procedures and participate in patient rehabilitation. Routine and advanced testing requires experience in exercise physiology, pulmonary rehab, sleep apnea evaluation, ventilation and methacholine challenge studies. A minimum of two years progressively responsible related experience coupled with two years of college or technical school, NBRC Certification (or registry preferred) and a valid NY City Board of Health Technologists (029) permit is required.

We offer an attractive salary and comprehensive benefits package. For consideration, send resume (resumes without salary history/requirements will not be considered) to our Technical Recruiter, PO Box 3999HR, New Hyde Park, NY 11042. *An Equal Opportunity Employer.*

LIJ Affiliation at
Queens Hospital Center

Long Island Jewish Medical Center,
The Long Island Campus for the
Albert Einstein College of Medicine

Circle 126 on reader service card

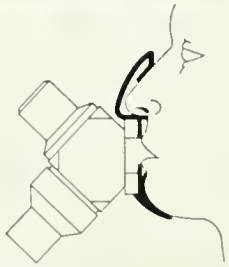
NEW RUDOLPH MOUTH/FACE MASK

Stress/Exercise/Pulmonary Testing,
and Metabolic Measurements.

T-Shape™ Valve

Y-Shape™ Valve

- The **New** Design of isolating the nose chamber reduces the masks rebreathing volume dead space.
- This lower dead space improves breath by breath measurements.



HANS RUDOLPH, inc.™

7200 Wyandotte • Kansas City, Missouri 64114 U.S.A.
(816) 363-5522 FAX (816) 822-1414
Toll Free within the U.S.A 1-800-456-6695

Circle 113 on reader service card

For your convenience, information, and direct access, the advertisers in this issue and their phone numbers are listed below. Please use this directory for requesting written material or for any questions you may have.

HELP LINES

Ambu Inc	800-AMBU INC
Automatic Liquid Packaging Inc	815-338-9500
Burroughs Wellcome	919-248-3000
CNS Inc	800-843-2978
Component Systems Inc	800-ISOLATE
DeVilbiss	800-DEV-1988
JH Emerson Co	800-252-1414
Hans Rudolph Inc	800-456-6695
HealthScan Products Inc	800-962-1266
HR Inc	800-426-1042
Impact Medical Corp	201-882-1212
Monaghan Medical Corp	800-833-9653
MSA Catalyst Research	800-672-4678
Peace Medical	800-537-9564
Puritan-Bennett Corp	800-255-6773
Quinton Instrument Co	800-426-0347
Ross Laboratories	614-227-3189
Schering Corp	201-298-4660
Sherwood Medical	800-325-7472
StarMed Staffing	800-STARMED

Notices of competitions, scholarships, fellowships, examination dates, new education programs, and the like will be listed here free of charge. Items for the Notices section must reach the Journal 60 days before the desired month of publication (January 1 for the March issue, February 1 for the April issue, etc). Include all pertinent information and mail notice to RESPIRATORY CARE Notices Dept, 11030 Ables Lane, Dallas TX 75229-4593.

Notices

THE ALLEN AND HANBURYS PUBLICATIONS AWARDS FOR 1991

1. $2,000 for the best original paper (study, evaluation, or case report) accepted for publication in RESPIRATORY CARE from November 1990 through October 1991.

2. Four awards of $1,000 each for papers based on 1990 OPEN FORUM presentations accepted for publication in RESPIRATORY CARE from November 1990 through October 1991.

3. Five awards of $500 each for the best papers (submitted, not necessarily published) from 'never published in RC' OPEN FORUM participants. The author must present the abstract at the Annual Meeting and must submit a paper based on the abstract *before* the Annual Meeting (received in the Editorial Office by December 1).

REGISTRATION REIMBURSEMENT FOR OPEN FORUM PAPERS

Any 1991 OPEN FORUM presenter (or co-author designee) who submits an adequately prepared paper based on his or her OPEN FORUM presentation *prior to* or *at* the 1991 Annual Meeting will be reimbursed for Annual Meeting registration. The submitted paper must contain complete data, be appropriately organized, and be typed double-spaced. Camera-ready artwork need not be submitted with the paper, but sketches of proposed figures should be clear and detailed enough to allow critique.

RADIOMETER AMERICA

Radiometer America Inc is offering three awards of $333 each for the best features from (1) Test Your Radiologic Skill, (2) Blood Gas Corner, and (3) PFT Corner accepted for publication from November 1990 through October 1991.

The awards will be made at the 1991 Annual Meeting. Papers are judged automatically. No application is necessary.

AARC ANNUAL CONVENTION SITES & DATES

1991—Atlanta, Georgia, December 7-10

1992—San Antonio, Texas, December 12-15

1993—Nashville, Tennessee, December 11-14

1994—Las Vegas, Nevada, December 12-15

1995—Orlando, Florida, December 2-5

PUBLICATION OF INTEREST

"Recommendations for Preventing Transmission of Human Immunodeficiency Virus and Hepatitis B Virus to Patients during Exposure-Prone Invasive Procedures." MMWR 1991;40 (No. RR-8).

Single copies of this document are available from the National AIDS Clearinghouse, PO Box 6003, Rockville MD 20850; telephone 800-458-5231.

THE NATIONAL BOARD FOR RESPIRATORY CARE

1991 Examination and Fee Schedule

CRTT Examination

EXAMINATION DATE:	JULY 20, 1991
Applications Accepted Beginning:	March 1, 1991
Application Deadline:	May 1, 1991
EXAMINATION DATE:	NOVEMBER 9, 1991
Applications Accepted Beginning:	July 1, 1991
Application Deadline:	September 1, 1991

RRT Examination

EXAMINATION DATE:	DECEMBER 7, 1991
Applications Accepted Beginning:	June 1, 1991
Application Deadline:	August 1, 1991

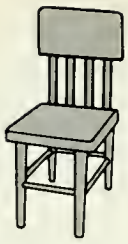
RPFT Examination

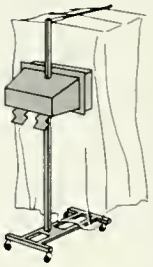
EXAMINATION DATE:	DECEMBER 7, 1991
Applications Accepted Beginning:	July 1, 1991
Application Deadline:	September 1, 1991

Fee Schedule

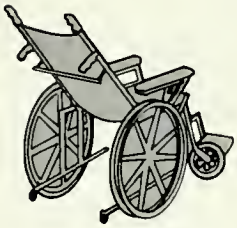
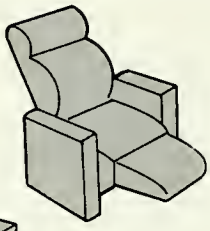
Entry Level CRTT—new applicant:	$ 75.00
Entry Level CRTT—reapplicant:	$ 50.00
RRT Written and Clinical Simulation—new applicant:	$175.00
Written Registry Only new applicant:	$ 75.00
Written Registry Only reapplicant:	$ 50.00
Clinical Simulation Only new and reapplicant:	$100.00
Entry Level CPFT—new applicant:	$100.00
Entry Level CPFT—reapplicant:	$ 80.00
Advanced RPFT—new applicant:	$150.00
Advanced RPFT—reapplicant:	$130.00
CRTT Recredentialing:	$ 25.00
RRT Recredentialing:	
Written Registry Examination	$ 25.00
Clinical Simulation Examination	$ 65.00
CPFT Recredentialing:	$ 25.00
RPFT Recredentialing:	$ 90.00
Membership Renewal CRTT/RRT/CPFT/RPFT	$ 12.00

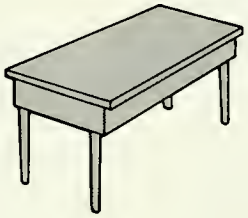
8310 Nieman Road • Lenexa, Kansas 66215 • (913) 599-4200

Anyone can do it in a chair.  But

with a DEMISTIFIER  you can

do it in a chair , in a wheelchair

 or in a recliner  , or you can

do it on a table  , or on a bed

, or even in a baby crib .

You can do it anywhere in a

hospital or at home . . .

administer aerosols with the

WRITE FOR FREE VIDEO TAPE

DEMISTIFIER™

ISOLATION CHAMBER

from

peace medical

50 South Center Street, Unit 11
Orange, New Jersey 07050
(201) 672-2120 • 800-537-9564
FAX: (201) 672-3404

Circle 123 on reader service card

RESPIRATORY CARE

Instructions for Authors and Typists

These Instructions are meant to guide authors and typists, including veterans in those roles, in the production of quality manuscripts. Perfection is not expected, but the well-prepared manuscript has the best chance for prompt review and early publication.

General Requirements

Submissions should (1) be related to respiratory care, (2) be planned for one of the publication categories below, and (3) be prepared as indicated in these Instructions. A letter accompanying the manuscript must specify the intended publication category, be signed by all the authors, and, when there are two or more authors, state that "We, the undersigned, have all participated in the work reported, read the accompanying manuscript, and approved its submission for publication."

Publication Categories

Research Article (Study): A report of an original investigation.
Evaluation of a Device/Method/Technique: A description and evaluation of an old or new device, method, technique, or modification.
Case Report: A report of a clinical case that is uncommon or of exceptional teaching value. The author(s) must have been associated with the case. A case-managing physician must be one of the authors or, if not an author, must supply a letter approving the manuscript.
Case Series: Like a Case Report but including a number of cases.
Review Article: A comprehensive, critical review of the literature and state of the art of a pertinent topic that has been the subject of 40 or more published research papers.
Overview: A critical review of a pertinent topic about which not enough research has been published to merit a Review Article.
Update: A report of subsequent developments in a topic that has been critically reviewed (not necessarily in this journal).
Point of View: A paper expressing the author's personal opinions on a pertinent topic.
Special Article: If a paper does not fit one of the foregoing categories but is pertinent, the editors may consider it as a Special Article.
Editorial: A paper that draws attention to a pertinent concern.
Letter: A signed communication about material published in this journal or on topics of interest or value to readers.
Blood Gas Corner: A brief, instructive case report (real or fictional) involving invasively or noninvasively obtained respiratory care blood data, followed by questions for readers—with answers and discussion.
PFT Corner: Like Blood Gas Corner but involving pulmonary function testing.
Test Your Radiologic Skill: Like Blood Gas Corner and PFT Corner but involving pulmonary-medicine radiography and including one or two 4 × 5 or 5 × 7 inch prints of radiographs. The case must be real.
Review of Book, Film, Tape, or Software: Anyone interested in writing a review can discuss it with an editor.

Editorial Consultation and Author's & Typist's Kit

To discuss a writing project, write to RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229 or call 214/243-2272.

Authors are urged to obtain the RESPIRATORY CARE Author's & Typist's Kit. The Kit provides *authors* with specific guidance about writing a research paper, writing a case report, converting to and from SI units, and in-house manuscript review. *Typists* can use the Kit's Model Manuscript, a list of journal name abbreviations, and a copy of these Instructions. The Kit is free from the Journal office.

Preparing the Manuscript

General Concerns—*Typist*

- Double-space ALL lines, including those in references, figure legends, and tables. Do not justify right margins.
- Number pages in upper right corner and leave margins of 1½" or more on all four sides of the page.
- For research articles, follow format of Model Manuscript, Respir Care 1984;29:182 (Feb 1984).
- Meticulously follow instructions for typing references.

General Concerns—*Author:*

- Structure manuscript as specified hereafter.
- Provide all requested information on title page as specified hereafter.
- Proofread manuscript for completeness, clarity, grammar, spelling; be sure all references, figures, and tables are cited in the text.
- Consider having paper reviewed in-house before submission.
- Have all co-authors proofread and approve manuscript and sign submission letter.

Manuscript Structure

Most kinds of papers have standard parts in a standard order. However, papers can vary individually, and not every paper will have all the parts listed here.

Research Article: Title page, abstract page, continuous text (Introduction, Materials & Methods, Results, Discussion), Product Sources page, Acknowledgments page, references, tables, figure legends. Please consult "Writing a Research Paper," Respir Care 1985;30:1057 (Dec 1985) and Model Manuscript, Respir Care 1984;29:182 (Feb 1984).
Evaluation of Device/Method/Technique: Title page, abstract page, continuous text (Introduction, Description of Device/Method/Technique, Methods of Evaluation, Results of Evaluation, Discussion), Product Sources page, Acknowledgments page, references, tables, figure legends.
Case Report or Case Series: Title page, abstract page, continuous text (Introduction, Case Summary, Discussion), Acknowledgments page, references, tables, figure legends. Also see "How To Write a Better Case Report," Respir Care 1982;27:29 (Jan 1982).
Review Article: Title page, Table of Contents page, continuous text (Introduction, History, Review of Literature, State of the Art, Discussion, Summary), references. May include figures & tables. No abstract. Table of Contents optional. Other formats may be appropriate.
Overview, Update, Point of View, or Special Article: Title page, text (introduction, message), references, tables, figure legends. No abstract.
Letter: Title page (provide a title), text, writer's name & affiliation, references. Tables & figures may be included. Double-space everything. Write "For Publication" on title page.

Structure: Important Details

Title Page: List title of paper, all authors' full names, degrees, credential letters, professional positions, and affiliations. List correspondence address, telephone number, and reprint address if desired. Name sources of grants or other support. Identify any author's consulting or commercial relationships that pertain to the paper's topic.

Abstract Page: Number this Page 1. List paper's title but omit authors' names. Abstract should be 200 words or less and must be informative, briefly specifying main points of paper, such as methods, results, and conclusions drawn.

Statistical Analysis: In research articles, identify statistical tests and chosen level of significance in the Methods section. In Results section, report actual P values.

Figures (illustrations): All photographs, diagrams, & graphs must be numbered as Figure 1, Figure 2, etc, according to the order in which each is first mentioned in the text. Photographs must be glossy prints 5 × 7 to 8 × 10 inches and should be black & white unless color is essential. Letters and numerals must be neat and large enough to remain legible if figure is reduced in size for publication. Final figures must be of professional quality, but 'rough' sketches may accompany the submitted manuscript, with final figures to be prepared after review. Identify each figure on back with a stick-on label showing figure number and arrow indicating top; omit author's name. Cover label with clear tape so ink will not smudge other prints. Supply three sets of unmounted figures. If figure has been published before, include copyright-holder's written permission to use it.

Figure Legends: List figure legends on a separate page, not on figures. If a figure has been published before, list the source in the legend.

Tables: Type each table on a separate page. Avoid more than 8 columns across. Continue a deep table on following pages. Give each table a number and descriptive title, placed above the table. Double-space ALL lines in tables, including column headings and footnotes.

Drugs: Brand names may be given, but always also show generic names.

Units of Measurement: In addition to conventional units of measure, show SI values and units in brackets after conventional expressions: ie, "PEEP, 10 cm H_2O [0.981 kPa]." For conversion to SI, see RESPIRATORY CARE 1988;33:861-873 (Oct 1988).

Commercial Products: If three or fewer commercial products are named in the text, list the manufacturer's name and location in parentheses the first time each is mentioned. If four or more products are named, do not list manufacturers in the text; instead, name the products and manufacturers in a Products Sources list at the end of the text. Provide model numbers when available.

Abbreviations: Use an abbreviation only if the term occurs several times in the paper. Write out the full term the first time it appears, followed by the abbreviation in parentheses. Thereafter, employ the abbreviation alone. Never use an abbreviation without defining it. Do not create new abbreviations unless absolutely necessary.

References:

- Use references to support statements of fact, indicate sources of information, or guide readers to further pertinent literature.
- Cite only published works—or works accepted for publication. When listing an accepted but still unpublished work, designate the accepting journal's name, followed by "(in press)."
- In the text, cite references by superscript numerals (half space above text), not in parentheses. The first reference cited in the text is number 1, the next is number 2, etc.
- In the reference list, place the cited works in numerical order.
- For the reference list, obtain author names, article and book titles, dates, volume and page numbers from the *original* cited articles and books, not from secondary sources such as other articles' reference lists, which often are inaccurate.
- Type references in medical-journal style. Examples appear at the end of these Instructions. Abbreviate journal names as in *Index Medicus*. A list of many journal-name abbreviations was published in Respir Care 1988;33:1050 (Nov 1988).
- DOUBLE-SPACE the lines of references.
- List ALL authors' names. Do not use "et al" to substitute for names.
- Identify abstracts, editorials, and letters as such. See examples.

Personal Communications, Unpublished Papers, and Unpublished Observations: List unpublished items in parentheses in the text, not in the reference list.

Examples of How To Type References

Notes: Although the examples here are printed with single-spaced lines, please double-space references in manuscripts. Also, note that words in article and book titles are not capitalized—except proper names.

Standard Journal Article:

1. Shepherd KE, Johnson DC. Bronchodilator testing: An analysis of paradoxical responses. Respir Care 1988;33:667-671.

Corporate Author Journal Article:

2. American Association for Respiratory Care. Criteria for establishing units for chronic ventilator-dependent patients in hospitals. Respir Care 1988;33:1044-1046.

Article in Journal Supplement:

(Journals differ in their methods of numbering and identifying supplements. Supply sufficient information to allow retrieval.)

3. Reynolds HY. Idiopathic interstitial pulmonary fibrosis. Chest 1986;89(3, suppl):139s-143s.

Abstract in Journal:

(Abstracts are not strong references; when possible, full papers should be cited. When cited, abstracts should be identified as such.)

4. Lippard DL, Myers TF, Kahn SE. Accuracy of pulse oximetry in severely hypoxic infants (abstract). Respir Care 1988;33:886.

Editorial in Journal:

5. Rochester DF. Does respiratory muscle rest relieve fatigue or incipent fatigue? (editorial). Am Rev Respir Dis 1988;138:516-517.

Letter in Journal:

6. Smith DE, Herd D, Gazzard BG. Reversible bronchoconstriction with nebulised pentamidine (letter). Lancet 1988;2:905.

Personal Author Book:

7. Nunn JF. Applied respiratory physiology. New York: Appleton-Century-Crofts, 1969.

Note: To specify pages cited in a book, place a colon after the year and then list the page(s). Examples: 1969:85 (one page), 1963:85-95 (series of contiguous pages), 1963:85,95 (separated pages).

Corporate Author Book:

8. American Medical Association Department of Drugs. AMA drug evaluations, 3rd ed. Littleton CO: Publishing Sciences Group, 1977.

Book with Editor, Compiler, or Chairman as 'Author':

9. Guenter CA, Welch MH, eds. Pulmonary medicine. Philadelphia: JB Lippincott, 1977.

Chapter in Book:

10. Pierce AK. Acute respiratory failure. In: Guenter CA, Welch MH, eds. Pulmonary medicine. Philadelphia: JB Lippincott, 1977:171-223.

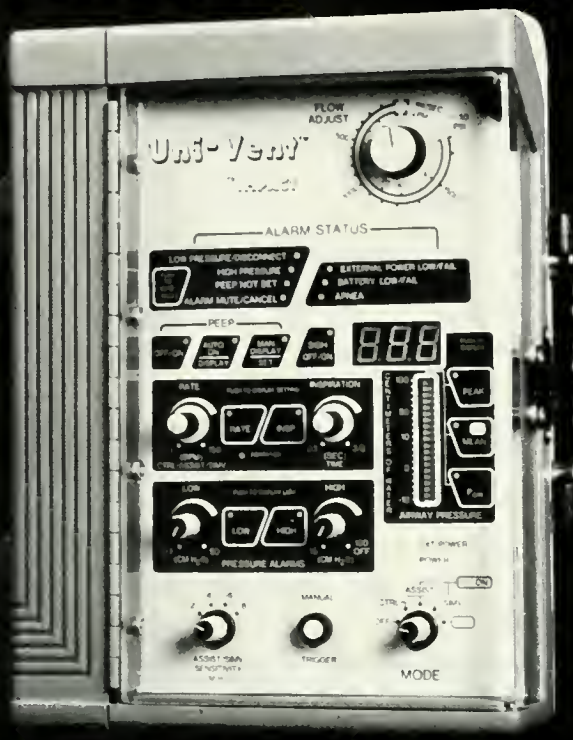
Submitting the Manuscript

After preparing the manuscript according to these Instructions, perform a final proofreading and check for accuracy and completeness. Then mail three copies of the manuscript and three sets of figures to RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229 (or Federal Express to RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229). Manuscript copy on IBM-compatible or Macintosh disks in addition to the requisite three hard copies will facilitate processing (Macintosh preferred). Enclose a letter as specified under **General Requirements** at the beginning of these Instructions. Do not submit material that has been published or is being considered elsewhere.

Author's Checklist

1. Is paper for a listed publication category?
2. Does cover letter meet specifications?
3. Is title page complete?
4. Are all pages double-spaced and numbered?
5. Are all references, figures, and tables cited in the text?
6. Are references typed in requested style?
7. Have SI values been provided?
8. Has all arithmetic been checked?
9. Has manuscript been proofread by all authors?

THE IMPACT OF THE FUTURE - TODAY!



Uni-Vent™ is a full spectrum critical care/trauma/transport ventilator. Its "smart" interactive design safely protects, monitors and provides your patient with a wide range of ventilatory care features.

Uni-Vent™ includes multiple operating modes, alarms and displays and weighs just 9-lbs! Its Assist-Control and SIMV modes, and optional electronic demand valve - are all PEEP compensated to reduce your patients' work-of-breathing. Gas- conserving electronics provide consistency, dependability and insure the maximum benefit from available portable gas sources - a must for transport applications!

Uni-Vent™: for your emergency, recovery, critical care and transport needs!

Circle 111 on reader service card

IMPACT MEDICAL CORP. 27 Fairfield Place, P.O. BOX 508, WEST CALDWELL, NJ 07006 201/882-1212

IISP

Blood Gas Study Packages

Patient Evaluation

☐ Arterial Blood Gas Interpretation
Item PE10-$10

Describes a systematic method that allows you to correctly classify the acid-base dysfunction and to relate the diagnosis concisely and coherently to other members of the health care team.

☐ Sources of Error in the Determination of Blood Gas Values and pH
Item PE7-$10

☐ Temperature Adjustment of Blood Gases and pH
Item PE8-$10

Shipping is $2 for the first copy and 25¢ for each additional copy.
Credit card orders may call (214) 243-2272.
To place an order, mail the completed order blank below to: AARC, 11030 Ables Lane, Dallas, TX 75229

Name _____
Address _____
_____

Check appropriate boxes:
☐ PE10 - $10 ☐ PE7 - $10 ☐ PE8 - $10
Shipping: $ _____ Total: $ _____

Mail to: American Association for Respiratory Care
11030 Ables Lane, Dallas, TX 75229

Authors in This Issue

Balmes, John R 1037
Chaisson, Richard E 1017
Dolovich, Myrna 931
Fallat, Robert J 1008
Giordano, Sam P 914
Herceg, Rosa 989
Hess, Dean 952
Kacmarek, Robert M 952
Kandal, Kathryn 1008
Matthys, Heinrich 989
McAvinue, Sharon 1017
Newman, Stephen P 939
Sly, R Michael 994
Svedmyr, Nils 922
Tashkin, Donald P 977
Waskin, Hetty 1026

Advertisers in This Issue

Ambu Inc 1048
Automatic Liquid Packaging Inc 903
Burroughs Wellcome 904a
CNS Inc 892
Component Systems Inc 907
DeVilbiss 1049
JH Emerson Co 1047
Hans Rudolph Inc 1050
HealthScan Products Inc 909
HR Inc 910
Impact Medical Corp 1055
Monaghan Medical Corp 894, 895, 911, 1045
MSA Catalyst Research 898
Peace Medical 1052
Puritan-Bennett Corp ..... Cover 2, 889
Quinton Instrument Co 890
Ross Laboratories 896, 897
Schering Corp ..... Cover 3, Cover 4
Sherwood Medical 900

Employment Opportunities:
StarMed Staffing 1047
Long Island Jewish Medical Center, New Hyde Park NY 1050

114 **Ambu Inc**
Res-Cue Key
116 **Automatic Liquid Packaging Inc**
ALP OPTI-MOL Humidifying System
115 **Burroughs Wellcome Co**
Exosurf
117 **CNS Inc**
Sleep Testing
118 **Component Systems Inc**
Core Curriculum on Tuberculosis
119 **DeVilbiss**
Aerosol Management
120 **JH Emerson Co**
Aerosol/Sputum Treatment Chamber
113 **Hans Rudolph Inc**
Mouth/Face Mask
109 **HealthScan Products Inc**
Low Range Peak Flow Meter
121 **HR Inc**
Aerosol Treatment Guard
111 **Impact Medical Corp**
Uni-Vent Ventilator
126 **Long Island Jewish Medical Center**
Employment
142 **Monaghan Medical Corp**
AeroVent Device
139 **Monaghan Medical Corp**
Aerochamber
106 **Monaghan Medical Corp**
Aerochamber with Mask
122 **MSA Catalyst Research**
MiniCap CO_2 Monitor
123 **Peace Medical**
Demistifier Isolation Chamber
108 **Puritan-Bennett Corp**
7200ae Ventilator
128 **Puritan-Bennett Corp**
7200ae Ventilator
105 **Quinton Instrument Co**
PFT System
124 **Ross Laboratories**
Beractant Intratracheal Suspension
112 **Schering Corp**
Proventil
125 **Sherwood Medical**
Voldyne Deep Breathing Exerciser
127 **StarMed Staffing**
Employment

AARC Information Requests or Change of Address

Please complete the card below

AARC Membership No. _____

Old Address

Name _____

Street _____

City/State/Zip _____

New Address

Street _____

City/State/Zip _____

Check the boxes below for information from the AARC

- ☐ Change of Address
- ☐ AARC Membership Info
- ☐ AARC Catalog
- ☐ AARC Position Statement

RESPIRATORY CARE

September Information Service **Expires December 31, 1991**

Name _____ Ph.# _____

Institution _____

Address _____

City/State/Zip _____

Please Circle No More Than 15 Items

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120
121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140
141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160

I. Type of Instn/Practice
1 ☐ Hosp 500 or more beds
2 ☐ Hosp 300 to 500 beds
3 ☐ Hosp 200 to 300 beds
4 ☐ Hosp 100 to 200 beds
5 ☐ Hosp 100 or less beds
6 ☐ Clinic/Group Practice
7 ☐ Independent RT Provider
8 ☐ Industry (Mfgr/Sales)

II. Department
A ☐ Respiratory Ther
B ☐ Cardiopulmonary
C ☐ Anesthesia Service
O ☐ Emergency Dept

III. Specialty
1 ☐ Clinical Practice
2 ☐ Perinatal Pediatrics
3 ☐ Critical Care
4 ☐ Clinical Research
5 ☐ Pulmonary Func Lab
6 ☐ Home Care/Rehab
7 ☐ Education
8 ☐ Management

IV. Position
A ☐ Dept Head
B ☐ Chief Therapist
C ☐ Supervisor
D ☐ Staff Technician
E ☐ Staff Therapist
F ☐ Educator
G ☐ Medical Director
H ☐ Anesthesiologist
I ☐ Other MD
J ☐ Nurse

V. Are you a member of the AARC?
1 ☐ Yes
2 ☐ No

RESPIRATORY CARE

September Information Service **Expires December 31, 1991**

Name _____ Ph.# _____

Institution _____

Address _____

City/State/Zip _____

Please Circle No More Than 15 Items

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120
121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140
141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160

I. Type of Instn/Practice
1 ☐ Hosp 500 or more beds
2 ☐ Hosp 300 to 500 beds
3 ☐ Hosp 200 to 300 beds
4 ☐ Hosp 100 to 200 beds
5 ☐ Hosp 100 or less beds
6 ☐ Clinic/Group Practice
7 ☐ Independent RT Provider
8 ☐ Industry (Mfgr/Sales)

II. Department
A ☐ Respiratory Ther
B ☐ Cardiopulmonary
C ☐ Anesthesia Service
D ☐ Emergency Dept

III. Specialty
1 ☐ Clinical Practice
2 ☐ Perinatal Pediatrics
3 ☐ Critical Care
4 ☐ Clinical Research
5 ☐ Pulmonary Func Lab
6 ☐ Home Care/Rehab
7 ☐ Education
8 ☐ Management

IV. Position
A ☐ Dept Head
B ☐ Chief Therapist
C ☐ Supervisor
D ☐ Staff Technician
E ☐ Staff Therapist
F ☐ Educator
G ☐ Medical Director
H ☐ Anesthesiologist
I ☐ Other MD
J ☐ Nurse

V. Are you a member of the AARC?
1 ☐ Yes
2 ☐ No

NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 2480 DALLAS, TX

POSTAGE WILL BE PAID BY ADDRESSEE

DAEDALUS ENTERPRISES INC
PO BOX 29686
DALLAS TX 75229-9691

NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 604 RIVERTON, NJ

POSTAGE WILL BE PAID BY ADDRESSEE

AARC PUBLICATIONS
P.O. BOX 1856
RIVERTON, NJ 08077-9456

NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 604 RIVERTON, NJ

POSTAGE WILL BE PAID BY ADDRESSEE

AARC PUBLICATIONS
P.O. BOX 1856
RIVERTON, NJ 08077-9456

Use these cards to request information from the AARC or advertisers in this issue.

IT'S THE EASY SOLUTION

Proventil®

(albuterol sulfate, USP)

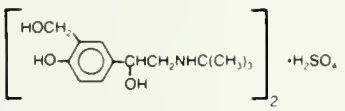
Solution for Inhalation

Unit Dose 0.083%*

0.5%* 20 mL bottle

*Potency expressed as albuterol

DESCRIPTION PROVENTIL, brand of albuterol sulfate, Solution for Inhalation, is a relatively selective $beta_2$-adrenergic bronchodilator (see **CLINICAL PHARMACOLOGY** section below). Albuterol sulfate has the chemical name α^1-[(*tert*-Butylamino) methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate (2:1) (salt), and the following chemical structure



Albuterol sulfate has a molecular weight of 576.7 and the empirical formula $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in ethanol.

The international generic name for albuterol base is salbutamol.

PROVENTIL Solution for Inhalation is available in two concentrations. The 0.5% solution is in concentrated form. Dilute 0.5 mL of the solution to 3 mL with normal saline solution prior to administration. The 0.083% solution requires no dilution prior to administration.

Each mL of PROVENTIL Solution for Inhalation (0.5%) contains 5 mg of albuterol (as 6.0 mg of albuterol sulfate) in an aqueous solution containing benzalkonium chloride, sulfuric acid is used to adjust the pH between 3 and 5. PROVENTIL Solution for Inhalation (0.5%) contains no sulfiting agents. It is supplied in 20 mL bottles.

Each mL of PROVENTIL Solution for Inhalation (0.083%) contains 0.83 mg of albuterol (as 1.0 mg of albuterol sulfate) in an isotonic aqueous solution containing sodium chloride and benzalkonium chloride, sulfuric acid is used to adjust the pH between 3 and 5. PROVENTIL Solution for Inhalation (0.083%) contains no sulfiting agents. It is supplied in 3 mL bottles for unit-dose dispensing.

PROVENTIL Solution for Inhalation is a clear, colorless to light yellow solution.

CLINICAL PHARMACOLOGY The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). The cyclic AMP thus formed mediates the cellular responses. *In vitro* studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on $beta_2$-adrenergic receptors compared with isoproterenol. While it is recognized that $beta_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, recent data indicate that 10 to 50% of the beta receptors in the human heart may be $beta_2$ receptors. The precise function of these receptors, however, is not yet established. Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or ECG changes.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.

Studies in asthmatic patients have shown that less than 20% of a single albuterol dose was absorbed following either IPPB or nebulizer administration, the remaining amount was recovered from the nebulizer and apparatus and expired air. Most of the absorbed dose was recovered in the urine 24 hours after drug administration. Following a 3.0 mg dose of nebulized albuterol, the maximum albuterol plasma level at 0.5 hour was 2.1 ng/mL (range 1.4 to 3.2 ng/mL). There was a significant dose-related response in FEV_1 and peak flow rate (PFR). It has been demonstrated that following oral administration of 4 mg albuterol, the elimination half-life was 5 to 6 hours.

Animal studies show that albuterol does not pass the blood-brain barrier. Recent studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

In controlled clinical trials, most patients exhibited an onset of improvement in pulmonary function within 5 minutes as determined by FEV_1. FEV_1 measurements also showed that the maximum average improvement in pulmonary function usually occurred at approximately 1 hour following inhalation of 2.5 mg of albuterol by compressor-nebulizer, and remained close to peak for 2 hours. Clinically significant improvement in pulmonary function (defined as maintenance of a 15% or more increase in FEV_1 over baseline values) continued for 3 to 4 hours in most patients and in some patients continued up to 6 hours.

In repetitive dose studies, continued effectiveness was demonstrated throughout the 3-month period of treatment in some patients.

INDICATIONS AND USAGE PROVENTIL Solution for Inhalation is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease and acute attacks of bronchospasm.

CONTRAINDICATIONS PROVENTIL Solution for Inhalation is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS As with other inhaled beta-adrenergic agonists, PROVENTIL Solution for Inhalation can produce paradoxical bronchospasm, which can be life threatening. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs and with the home use of sympathomimetic nebulizers. It is, therefore, essential that the physician instruct the patient in the need for further evaluation if his/her asthma becomes worse. In individual patients, any $beta_2$-adrenergic agonist, including albuterol solution for inhalation, may have a clinically significant cardiac effect.

Immediate hypersensitivity reactions may occur after administration of albuterol as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema.

PRECAUTIONS General: Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension, in patients with convulsive disorders, hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.

Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Additionally, beta-agonists, including albuterol, when given intravenously may cause a decrease in serum potassium, possibly through intracellular shunting. The decrease is usually transient, not requiring supplementation. The relevance of these observations to the use of PROVENTIL Solution for Inhalation is unknown.

Information For Patients: The action of PROVENTIL Solution for Inhalation may last up to 6 hours and therefore it should not be used more frequently than recommended. Do not increase the dose or frequency of medication without medical consultation. If symptoms get worse, medical consultation should be sought promptly. While taking PROVENTIL Solution for Inhalation, other antiasthma medicines should not be used unless prescribed.

Drug Interactions: Other sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with albuterol.

Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of albuterol on the vascular system may be potentiated.

Beta-receptor blocking agents and albuterol inhibit the effect of each other.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Albuterol sulfate, like other agents in its class, caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium in a 2-year study in the rat, at oral doses corresponding to 10, 50, and 250 times the maximum human nebulizer dose. In another study this effect was blocked by the coadministration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice and a lifetime study in hamsters revealed no evidence of tumorigenicity. Studies with albuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility.

Teratogenic Effects—Pregnancy Category C: Albuterol has been shown to be teratogenic in mice when given subcutaneously in doses corresponding to the human nebulization dose. There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A reproduction study in CD-1 mice with albuterol (0.025, 0.25, and 2.5 mg/kg subcutaneously corresponding to 0.1, 1, and 12.5 times the maximum human nebulization dose, respectively) showed cleft palate formation in 5 of 111 (4.5%) of fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) of fetuses at 2.5 mg/kg. None were observed at 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) of fetuses treated with 2.5 mg/kg isoproterenol (positive control). A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) of fetuses at 50 mg/kg corresponding to 250 times the maximum human nebulization dose.

Labor and Delivery: Oral albuterol has been shown to delay preterm labor in some reports. There are presently no well-controlled studies which demonstrate that it will stop preterm labor or prevent labor at term. Therefore, cautious use of PROVENTIL Solution for Inhalation is required in pregnant patients when given for relief of bronchospasm so as to avoid interference with uterine contractibility.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of albuterol solution for inhalation in children below the age of 12 years have not been established.

ADVERSE REACTIONS The results of clinical trials with PROVENTIL Solution for Inhalation in 135 patients showed the following side effects which were considered probably or possibly drug related:

Central Nervous System: tremors (20%), dizziness (7%), nervousness (4%), headache (3%), insomnia (1%).

Gastrointestinal: nausea (4%), dyspepsia (1%).

Ear, Nose and Throat: pharyngitis (<1%), nasal congestion (1%).

Cardiovascular: tachycardia (1%), hypertension (1%).

Respiratory: bronchospasm (8%), cough (4%), bronchitis (4%), wheezing (1%).

No clinically relevant laboratory abnormalities related to PROVENTIL Solution for Inhalation administration were determined in these studies.

In comparing the adverse reactions reported for patients treated with PROVENTIL Solution for Inhalation with those of patients treated with isoproterenol during clinical trials of 3 months, the following moderate to severe reactions, as judged by the investigators, were reported. This table does not include mild reactions.

Percent Incidence of Moderate To Severe Adverse Reactions

Reaction	Albuterol N = 65	Isoproterenol N = 65
Central Nervous System		
Tremors	10.7%	13.8%
Headache	3.1%	1.5%
Insomnia	3.1%	1.5%
Cardiovascular		
Hypertension	3.1%	3.1%
Arrhythmias	0%	3.0%
**Palpitation	0%	22.0%
Respiratory		
*Bronchospasm	15.4%	18%
Cough	3.1%	5%
Bronchitis	1.5%	5%
Wheeze	1.5%	1.5%
Sputum Increase	1.5%	1.5%
Dyspnea	1.5%	1.5%
Gastrointestinal		
Nausea	3.1%	0
Dyspepsia	1.5%	0
Systemic		
Malaise	1.5%	0

*In most cases of bronchospasm, this term was generally used to describe exacerbations in the underlying pulmonary disease.

**The finding of no arrhythmias and no palpitations after albuterol administration in this clinical study should not be interpreted as indicating that these adverse effects cannot occur after the administration of inhaled albuterol.

Rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema have been reported after the use of inhaled albuterol.

OVERDOSAGE Manifestations of overdosage may include anginal pain, hypertension, hypokalemia and exaggeration of the pharmacological effects listed in **ADVERSE REACTIONS.**

The oral LD_{50} in rats and mice was greater than 2,000 mg/kg. The inhalational LD_{50} could not be determined.

There is insufficient evidence to determine if dialysis is beneficial for overdosage of PROVENTIL Solution for Inhalation.

DOSAGE AND ADMINISTRATION The usual dosage for adults and children 12 years and older is 2.5 mg of albuterol administered 3 to 4 times daily by nebulization. More frequent administration or higher doses is not recommended. To administer 2.5 mg of albuterol, either dilute 0.5 mL of the 0.5% solution for inhalation to a total volume of 3 mL with normal saline solution, or administer the contents of one unit-dose bottle (3 mL of 0.083% nebulizer solution) by nebulization. The flow rate is regulated to suit the particular nebulizer so that the PROVENTIL Solution for Inhalation will be delivered over approximately 5 to 15 minutes.

The use of PROVENTIL Solution for Inhalation can be continued as medically indicated to control recurring bouts of bronchospasm. During treatment, most patients gain optimum benefit from regular use of the nebulizer solution.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately, as this is often a sign of seriously worsening asthma which would require reassessment of therapy.

HOW SUPPLIED PROVENTIL Solution for Inhalation, 0.5%, is a clear, colorless to light yellow solution, and is supplied in bottles of 20 mL (NDC-0085-0208-02) with accompanying calibrated dropper, boxes of one. **Store between 2° and 25°C (36° and 77°F).**

PROVENTIL Solution for Inhalation, 0.083%, is a clear, colorless to light yellow solution, and is supplied in unit-dose bottles of 3 mL each, boxes of 25 (NDC-0085-0209-01.) **Store between 2° and 25°C (36° and 77°F).**

Schering Corporation
Kenilworth, NJ 07033 USA

Revised 1/90 13934339

Copyright © 1986, 1987, 1990, Schering Corporation. Kenilworth, NJ 07033. All rights reserved.

Circle 112 on reader service card

THE *ONLY* UNIT DOSE ALBUTEROL SULFATE

IT'S THE EASY SOLUTION

Proventil
(albuterol sulfate, USP)
Solution for Inhalation
Unit Dose 0.083%*
0.5%* 20 mL bottle
*Potency expressed as albuterol

Please see full prescribing information on adjacent page.

Copyright © 1991, Schering Corporation
All rights reserved
PN-073/16298406 2/91 Printed in U.S.A.

Schering®
Schering Corporation
Kenilworth, NJ 07033